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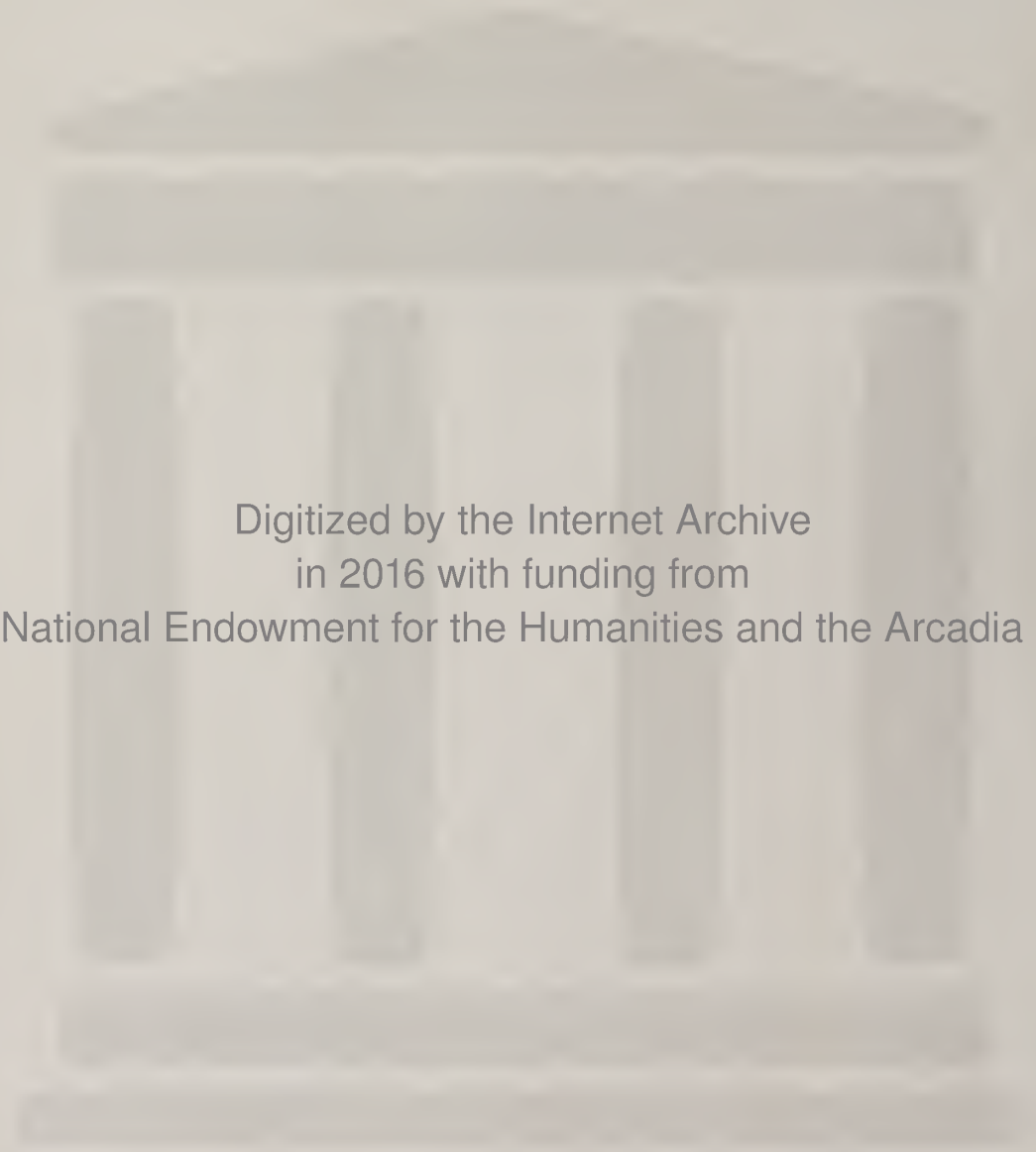


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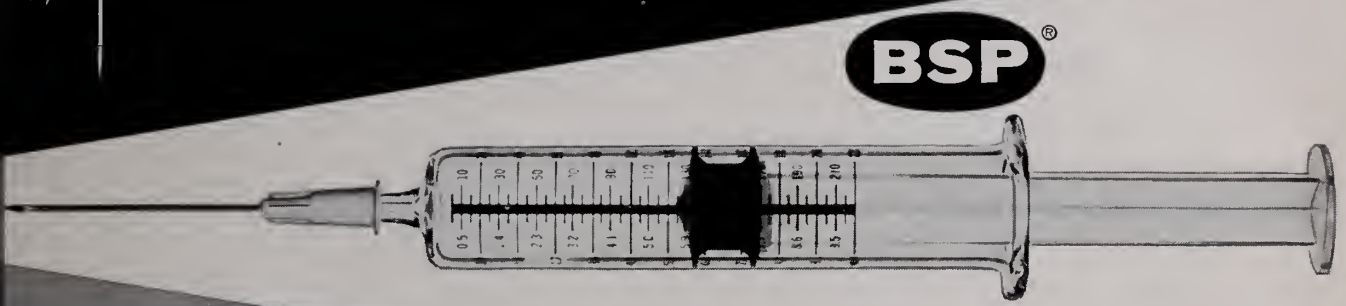
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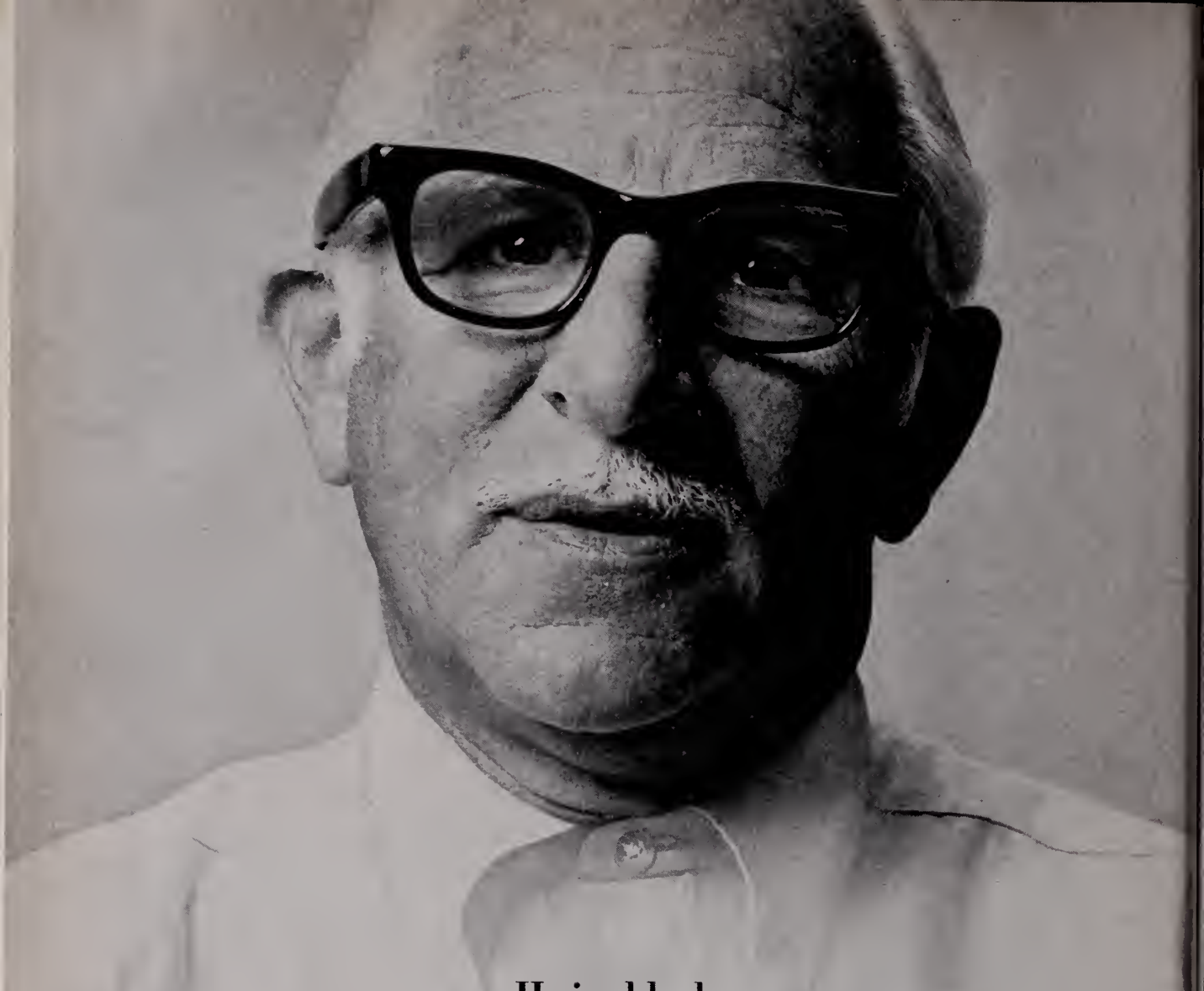
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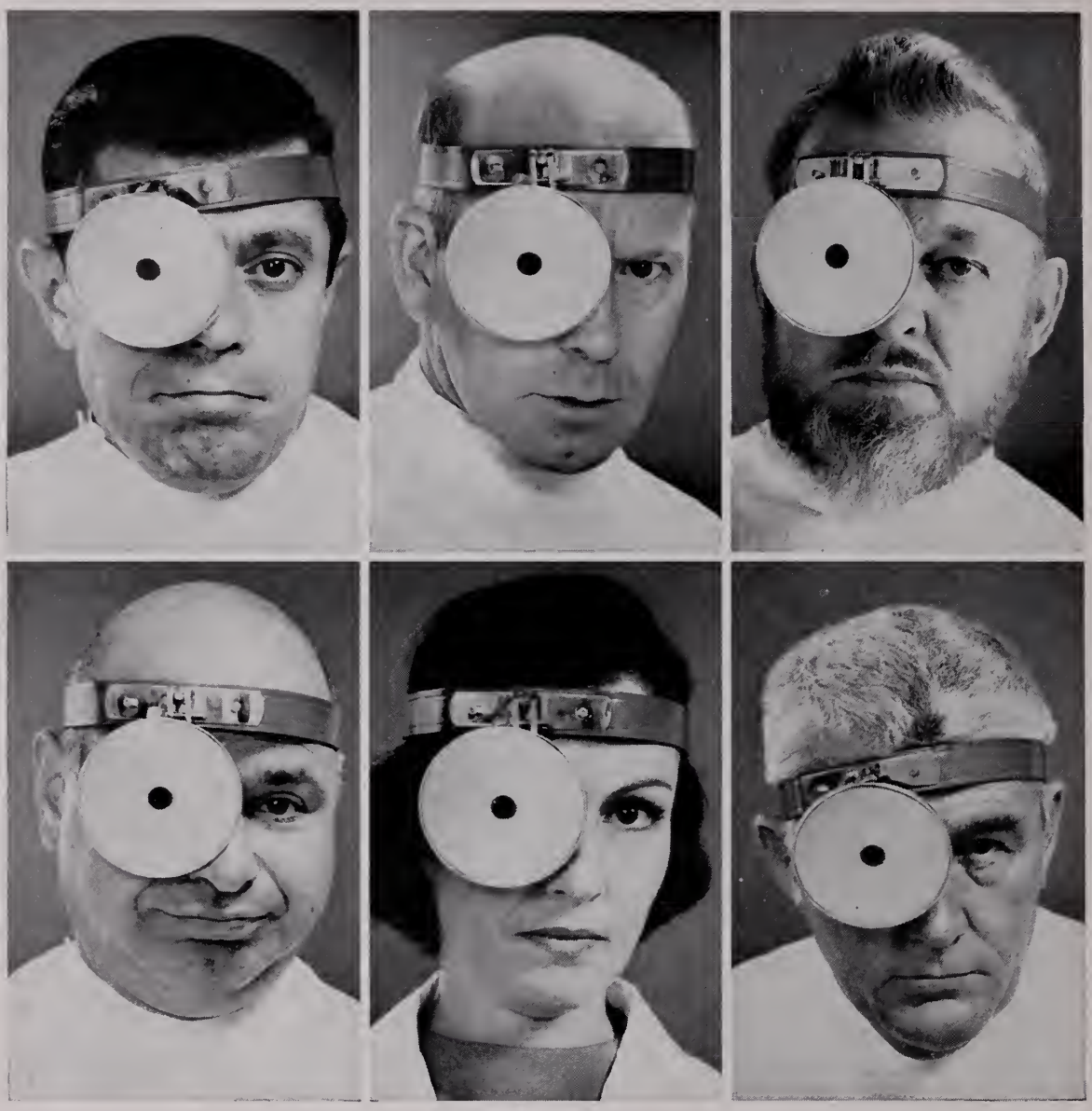
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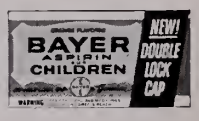
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See the President's Letter, Page 7

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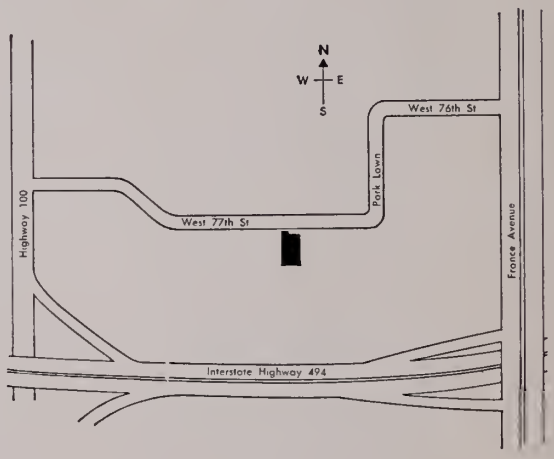
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President's Letter

EVERY PHYSICIAN is very much aware of the rising costs of health care and he knows or should know that the profession is under fire not only from Federal and State governments for this rise in health care costs, but from the public as well. The impact of Federal health care financing and the ever mounting government control over facets of health and medical costs are becoming more and more apparent. For instance, the *Welfare* cost of health care in Minnesota in the fiscal year 1969-70 is estimated to be in the neighborhood of $108 million as compared to a cost of $50 million for a similar twelve month period in 1966-67. Of this cost roughly 48% will be paid to nursing homes, 21% to hospitals, 8 to 10% to physicians and 11 to 13% for other services or goods. This increase in health care costs is fairly typical for the entire country.

Prior to the enactment of the Medicare and Medicaid laws, the appropriate committees of both the Senate and the House were strongly informed by representatives of organized medicine that their estimates of health care costs were much too low and that the Congress should look at costs of health care more realistically. However, this advice fell on deaf ears. Now that organized medicine's prediction of the high cost of these programs has come true, physicians are, nevertheless, being blamed and harassed for this increase.

We must find solutions to the problem of health care costs and take a positive position through constructive programs. It therefore becomes absolutely necessary that all physicians become actively engaged in programs to control and lower health care costs, if possible, while at the same time guarding against diminishing the quality of medical care. One way to do this is first to take a hard look at utilization of hospital and nursing home beds as well as to review the quality of medical care and its cost. The Federal government had this in mind when the Medicare and Medicaid Acts were passed in 1965; provision was made in the law to require utilization and review committees. It must be pointed out in clear terms that utilization and review are not new. Medical staffs have had various committees such as Records, Tissue, Audit and Utilization functioning for many years and long before the present Federal health plans. We have always been vitally concerned about the quality and standards of medical care since organized medicine began in the United States in the mid-nineteenth century.

It becomes apparent that some standardized approach to utilization-review is going to be required so that these vast programs and planning projects can acquire statistically valid information. We are going to have to agree on some kind of uniform approach to utilization review.

For this reason the Minnesota State Medical Association through its Subcommittee on Standards of Medical Care of the Committee on Medical Services and with the approval of the House of Delegates is in the process of working out a state-wide central organization to make utilization and review services available to physicians and hospitals.

In the President's Letter of next month plans of this new organization will be outlined in more detail.

Delmar R. Gillespie, M.D.
President
Minnesota State Medical Association

259172
JUL 16 1971

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Valium as an Adjunct to Cystoscopy*

CLYDE E. BLACKARD, M.D.†
ALEXANDER M. McBRIDE, M.D.†
JOHN J. WEDGE, M.D.†
GEORGE T. MELLINGER, M.D.†
Minneapolis, Minnesota

Prior to September 1, 1967, patients undergoing cystoscopic examination at the Minneapolis Veterans Administration Hospital received topical urethral anesthesia, either alone or in combination with intravenous Nisentil‡. Xylocaine¶ in a two per-cent solution was the topical anesthetic agent of choice. We noted, however, that neither topical Xylocaine nor intravenous Nisentil, alone or in combination, provided consistently good results in terms of patient comfort and ease of instrumentation.

Material and Method

Nisentil Intravenous

Nisentil is recommended as an analgesic agent for use in short urological procedures. It is a rapid-acting synthetic analgesic drug. When administered intravenously, its effects are apparent within one to two minutes and last for 30 to 60 minutes. The untoward effects of Nisentil noted on our service included nausea, vomiting, hypotension, weakness, restlessness, and confusion. Significant respiratory depression was not observed. Nisentil 30 mg. was administered intravenously immediately before the cystoscopic examination. During the period of analgesia, the patients remained awake, alert, and usually cooperative. In many cases patients frequently experienced pain and were unrelaxed, making instrumentation difficult. To find a more suitable supplementary agent to use with topical Xylocaine, we designed a study incorporating intravenous Nisentil, intravenous Valium§ and an intravenous placebo.

Valium Intravenous

Valium is principally a tranquilizer which

*Read at the North Central Section meeting of the American Urological Association in Rochester, Minnesota, on Thursday, September 19, 1968.

†Department of Urology, Veterans Administration Hospital, and the Department of Urology, University of Minnesota, Minneapolis, Minnesota.

‡Alphaprodine hydrochloride.
¶Lidocaine hydrochloride.
§Diazepam.

relieves tension and anxiety. In addition to its calming effect, it can cause amnesia and may relieve skeletal muscle spasm. No accurate details are available concerning its analgesic properties. Following intravenous injection, the onset of action is within 30 seconds and lasts from 20 minutes to one hour. Untoward effects of Valium include transient hypotension, respiratory depression, and muscular weakness. Because of its central depressant effect, Valium should not be administered to a patient in coma or in shock. If a patient is receiving another central nervous system depressant drug, the dose of Valium should be reduced. As Valium may cause increased cough reflex and laryngospasm, it is not recommended for bronchoscopy and laryngoscopy.

Although a valid comparison between Nisentil, an analgesic agent, and Valium, a tranquilizer, cannot be made, we did employ both drugs in our study to determine which one is a better supplementary agent for cystoscopic examination. The following agents were tested on 288 consecutive male patients undergoing cystoscopy as indicated in Table 1.

TABLE 1.
Number of Patients and Median Age in Each of the Four Study Groups

Drug	No. of Patients	Median Age
Valium 5 mg.	71	64 (24 to 80)
Valium 10 mg.	72	61 (22 to 80)
Nisentil 30 mg.	74	62 (29 to 84)
Placebo 2 cc Normal Saline	71	67 (42 to 86)
TOTAL	288	63 (22 to 86)

Topical Xylocaine

Two percent Xylocaine was applied topically to the urethra in all cases. Immediately before the cystoscopic examination, one of the above agents was randomly selected and administered intravenously. All four agents were employed in double blind fashion, and immediately after completion of the procedure various parameters were evaluated. Vital signs were recorded prior to the examination and immediately after administration of the drugs.

All examinations entailed at least cystoscopy. In addition to an urethrocystoscopic examination, urethral dilatation, retrograde pyelography, or split renal function studies were occasionally performed. In one instance, litholapaxy* was performed for a small bladder calculus.

Results

Side Effects

Along with changes in blood pressure and respiration, we observed the highest incidence of nausea, vomiting, weakness, and diaphoresis from Nisentil while the 10 mg. dose of Valium along with the placebo caused the lowest (Table 2).

TABLE 2.
Side Effects of the Four Drugs Tested

Drug	Nausea & Vomiting	Weakness	Diaphoresis	Total & Percent
Nisentil 30 mg.	7	17	3	27/74 = 36%
Valium 5 mg.	0	7	0	7/71 = 10%
Placebo 2 cc. Normal Saline	1	3	1	5/71 = 7%
Valium 10 mg.	1	3	0	4/72 = 6%

Bladder Spasm

Bladder spasm is a frequent problem encountered during cystoscopy and its presence usually precludes a satisfactory examination. Those patients receiving the 10 mg. dose of Valium had the lowest incidence of bladder spasm (Table 3).

TABLE 3.
Incidence of Bladder Spasm

Drug	No. with Bladder Spasm	Percent
Placebo 2 cc. Normal Saline	23/71	32%
Nisentil 30 mg.	19/74	26%
Valium 5 mg.	14/71	20%
Valium 10 mg.	5/72	7%

Vital Signs

Vital signs were recorded immediately before and two to three minutes following injection. They were also recorded at the com-

*See Test Your Word Score Page 45.

pletion of the endoscopic procedure (Table 4). For purposes of comparison, we arbitrarily defined as significant a fluctuation in blood pressure of more than 20 millimeters of mercury systolic or 10 millimeters of mercury diastolic, and a change in respiration of more than 10 breaths per minute. Nisentil 30 mg. caused a significant blood pressure fluctuation in 30 percent of the patients, while Valium 5 mg. had the least effect. Nisentil occasionally caused a drop in systolic blood pressure up to 40 millimeters of mercury. Valium in the 10 mg. dose would sometimes cause marked transient respiratory depression. This dose of

TABLE 4.
Effects on Vital Signs

Drug	No. With Blood Pressure Changes	Percent	No. with Respiratory Changes	Percent
Nisentil 30 mg.	22/74	30%	2/74	3%
Placebo 2 cc. Normal Saline	10/71	14%	2/71	3%
Valium 10 mg.	7/72	10%	13/72	18%
Valium 5 mg.	5/71	7%	8/71	11%

Valium produced a significant fluctuation in respiration in 18 percent of the patients, while Nisentil and the placebo had the least effect. Both hypotension and respiratory depression were related to the rapidity of injection, and in each instance returned to pre-injection levels without treatment.

Rating

Immediately following each procedure, the response of the patient was given a rating by each cystoscopist according to Table 5.

TABLE 5.
Rating of Patient's Response

Excellent	—Totally relaxed with no pain or spasm.
Good	—Good relaxation with mild discomfort, but the procedure accomplished easily.
Fair	—Poor relaxation with moderate pain or some minor difficulty in accomplishing the procedure.
Poor	—Considerable pain or spasm with no relaxation or extreme difficulty in accomplishing the procedure.

The results of the study have shown that Valium in the 10 mg. dose is superior to the other three agents (Table 6). This dose gave excellent results in 71 percent of the patients and was rated as poor in only three percent. In contrast, Nisentil was assigned a rating of excellent in 35 percent and poor in 20 percent. Using the chi-square test, a statistically significant difference was noted in the comparison of the four agents.

TABLE 6.
Overall Results of Study

Drug	No. Patients	Excellent	Good	Fair	Poor
Valium 10 mg.	72	51 (71%)	11 (15%)	8 (11%)	2 (3%)
Valium 5 mg.	71	28 (39%)	10 (29%)	12 (17%)	11 (15%)
Nisentil 30 mg.	74	26 (35%)	22 (30%)	11 (15%)	15 (20%)
Placebo 2 cc. Normal Saline	71	24(34%)	18 (25%)	13 (18%)	16 (23%)

Conclusion

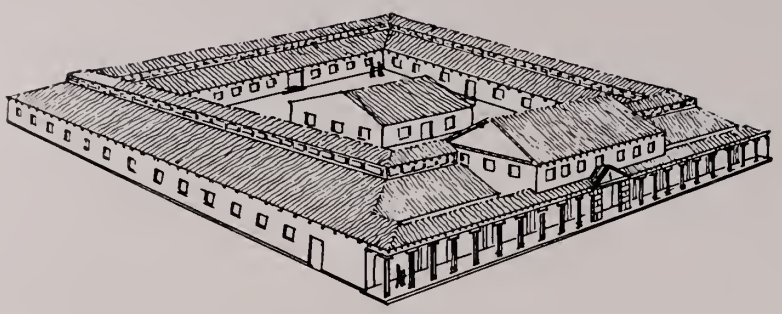
The urology staff at the Minneapolis Veterans Administration Hospital has been so pleased with Valium, that the 10 mg. dose is now used almost exclusively in our outpatient clinic. Since September, 1967, and up to February, 1969, nearly 2,000 cystoscopic examinations have been performed using a combination of topical Xylocaine anesthesia and intravenous Valium. Many of the patients have had total amnesia as well as analgesia. A transient respiratory depression may be obtained if the dose is too large or administration too rapid. We feel that there are few, if any, contraindications to the use of the drug aside from drug sensitivity, but we do recommend a smaller dose in debilitated patients. In younger males, we have had good results using up to 25 mg. intravenously. We do not advise that the patient drive an automobile for at least two hours following administration of the drug. We continue to find that intravenous Valium, usually in a 10 mg. dose, is a useful and more than satisfactory supplementary agent for cystoscopic and biopsy procedures.

My soul tasted that heavenly food which gives new appetite.—Dante.

FEATURE SPECIAL

Historic Hospitals

ROMAN MILITARY HOSPITALS



Restoration of the Roman Military Hospital at Vindonissa.
(Courtesy of Ciba Symposia, formerly published by Ciba Pharmaceutical Company, Summit, New Jersey, by permission.)

Although institutions devoted to the care of the sick are known to have existed in ancient China and India, the development of the hospital system is essentially a contribution of the Romans. The Roman genius for organization and the needs of the far-flung Roman military establishment resulted in a network of military hospitals located strategically throughout the Empire.

A number of these have been excavated, revealing a characteristic design consisting of concentric rows of rooms arranged about a rectangular enclosure reminiscent of later Spanish architecture. Pictured is a reconstruction made after investigation of the ruins of the Roman military hospital at Vindonissa (the modern Windisch) in Switzerland.

The hospital was located at the center of the military base and adjacent to the public bath which served the entire post. It was constructed of stone and built about 50 A.D. Its external dimensions were approximately 220 by 200 feet. The main building consisted of rows of rooms arranged on either side of a rectangular corridor. The rooms, measuring about 15½ by 11½ feet, were arranged in pairs with entry from a small common anteroom opening into the corridor. Assuming eight patients per room, the capacity of the hospital was 480.

Plumbing consisted of a single masonry drain-pipe which may have been connected to the latrines. Heating was by portable coal-burning stoves. A single large closet was provided for each pair of rooms. The small rectangular building in the center of the inner court consisted of a single room, and is believed to have been the treatment room.

The military base at Vindonissa was abandoned about 400 A.D.*

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*Simonet, Ciba Symposia I, 292, 1939.
Singer: From Magic to Science. Dover Publications, 1958.

Action is the prayer that's always answered.—Albert Hubbard.

Congenital Dislocation of the Hip*

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TREATMENT OF the newborn with congenital dislocation of the hip usually requires simple splinting for a few months and is generally successful, while, as the child becomes older, treatment becomes progressively more difficult. Over the age of 18 months surgery is often necessary; even then complete restoration to normal hips is often impossible. Early diagnosis in the newborn requires searching for (telescoping) instability of the hip; if one is to make the diagnosis before 18 months, he must look for such telescoping on routine examination and not wait for a limping gait to develop.

It has been pointed out by Hodgson and others that all newborn infants have lax capsular and ligamentous structures at birth. Were one searching for a predisposition to congenital displacement of the femoral head, excessive laxity of the capsular structures due to unknown neonatal influences would have to be considered. The initial extension of the hip joint would seem to be the first or primary mechanism in what may subsequently become a subluxation or a frank dislocation. Although such extension usually occurs at or immediately after delivery of the newborn, it is possible in malposition of the fetus that it could occur prenatally; also one cannot deny the possibility of a teratogenic dislocation.

Diagnosis in the Infant (zero to two years)

The observed dysplasia and hypoplasia of the bony elements in the infant hip are probably secondary changes to the displaced position of the femoral head, and *not* primary. The diagnostic signs are readily detected on clinical examination: (1) Telescoping (probably the most dependable diagnostic sign); (2) limited abduction (not in the newborn); (3) shortening; (4) extra skin creases (neither a constant finding nor entirely diagnostic when present); (5) x-ray confirmation of diagnosis.

*The Hip Service at Gillette State Hospital.

Ortolani's Sign

When present, this sign is important. It is present, however, only in complete dislocation of the hip and its significance lies in the fact that it indicates gross instability. The click occurs both with entrance and exit of the femoral head from the acetabulum; in the presence of very tight adductors, however, it frequently cannot be demonstrated as it is impossible to manipulate the head in and out of the socket. For this reason it loses its "positive" quality anywhere from one to six weeks after birth (Figures 1a, 1b).

Treatment in Infants (zero to two years)

This is the ideal period to successfully treat congenital dislocation. Needless to say, such an opportunity must be predicated on early accurate diagnosis.

Frog-Leg Position

In the *newborn,* one needs only to place the head within the acetabulum and hold it there for a brief period until the lax capsular and the ligamentous structures have had a chance to "tighten up." This can be done without anesthesia as a rule and the Lorenz or frog-leg position is to be recommended to the complete exclusion of internal rotation at this age level. Immobilization for one month in a full bilateral plaster cast (Figure 2) is usually sufficient at this age, and some feel the Von Rosen splint is all right instead of a cast, if supervision is adequate.

Older infants may require several months of casting until the hip is stable. Thereafter an abduction brace such as described by Hewson, Ponsetti, or Von Rosen is fitted and worn day and night until the infant is old enough to walk. Thereafter it is used as a night splint until the hip is considered normal.

Traction

Bilateral skin traction is indicated in the infant if treatment has been delayed long enough to permit shortening of the capsule and ligamentous structures. Children over three or four years of age require skeletal traction, depending on their size and weight. If at the time of immobilization in the Lorenz position the adductors are still tight, then subcutaneous tenotomy is recommended. In any event, traction should be continued *until the natal laxity of the capsular structure has been established.*



Fig. 1-a—The examiner holds the pelvis with one hand, while pushing backward, so if the hip is unstable, it will subluxate.

Treatment of Avascular Necrosis

Avascular necrosis in the treatment of congenital dislocation is entirely different from that seen in Legg-Perthes' disease. It is due to pressure necrosis, and the most common compressing force is tightness of the adductors. The hip should never be forced into abduction, and the Lorenz position is *not,* as some people mistakenly picture it, a right-angle immobilization. On the contrary, flexion should be more than a right angle, probably 100°, and the abduction should seldom, if ever, be more than 60°; in any event it should *never* be forced. If avascular necrosis does occur, it



Fig. 1-b—The examiner then abducts the hip, while feeling if the subluxed hip "jerks" back into the acetabulum.

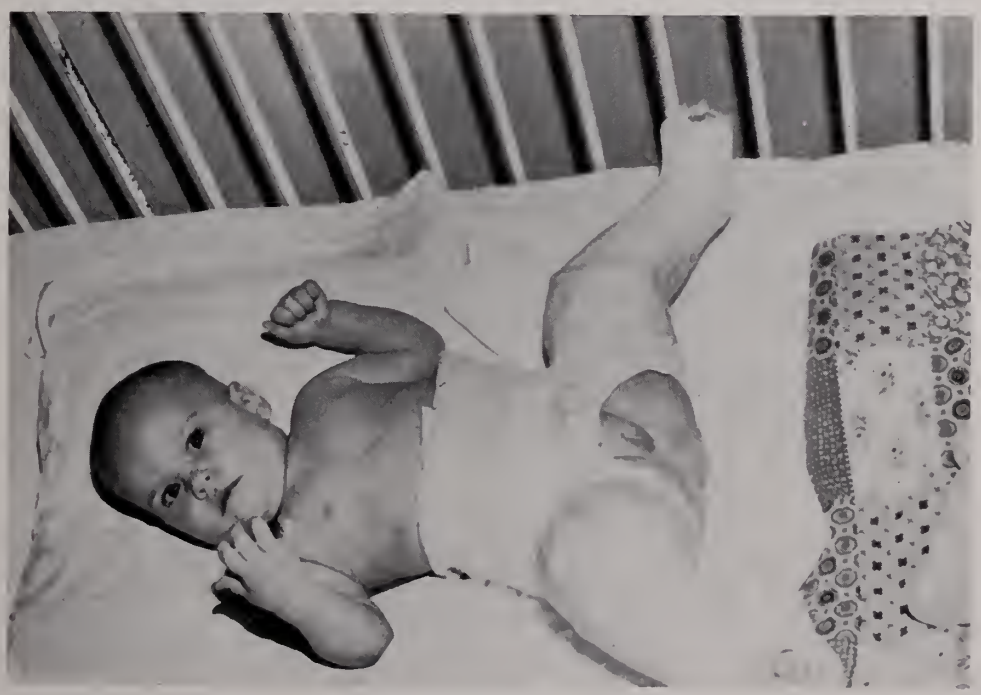


Fig. 2—Frog-leg position.

should be ignored and the treatment of the congenital hip continued as originally planned. Provided further compression is avoided and the basic rules of immobilization followed by mobilization are adhered to, the proximal femoral epiphysis will revascularize and minimal deformity, if any, will result provided the head is maintained in the acetabulum where it properly belongs. However, deformity can be avoided completely by adequate traction and non-forced reduction.

Surgery

There is no indication for surgery in the treatment of congenital dislocations in infants up to three months of age, the one possible exception being a teratogenic hip which by definition is a prenatal anomaly. This should raise the question: "How old is the dislocation," rather than "How old is the infant?" However, surgical intervention may be necessary if inadequate reduction persists after three months of age. Stability in the reduced position is the goal! The sooner it is established, the better the results!

Treatment in the Older Child

Even up to three or four years of age closed reduction and immobilization in the Lorenz position may occasionally be successful. The older child requires prolonged preliminary skeletal traction, adductor tenotomy, and gentle manipulative reduction under general anesthesia. Subsequent immobilization in the Lorenz position should be continued until a normal hip joint has been molded in the bony and cartilaginous anlage for the acetabulum. However, after 18 months of age, the potential for reversal of the acetabular dysplasia lessens and, due to the abnormal *direction* of the acetabulum, the hips tend to be unstable. For these reasons, treatment in the older child frequently requires operative management, regardless of prolonged immobilization.

Operative Management

General Considerations

In attempting open reduction of the dislocated hip, one must anticipate opening the capsule and freeing those soft tissue elements that constitute obstruction to closed reduction. The limbus so frequently blamed for preventing reduction should *not* be excised. Its presence helps to deepen the acetabulum and provides stability for the reduced head. It may, on occasion, have to be divided transversely but should not be sacrificed. On the contrary, the most frequent obstacle to reduction is an adherent capsule inferiorly along the *lower* border of the acetabulum. Once this adherent capsule has been dissected off the acetabulum, reduction of the head is usually easy, although occasionally some residual soft tissues must be removed from the depths of the socket. Before closing the capsule, advantage should be taken of the opportunity to excise the redundant capsule, much as the surgeon might do in dealing with the redundant sack of an inguinal hernia.

Shelf Operation

A pure shelf operation in the treatment of congenital dislocation of the hip is seldom adequate. An over-hanging shelf or roof will melt away all too frequently unless it is subjected to adequate stress and strain. Too much pressure against an over-hanging shelf will result in pressure necrosis of the capital femoral epiphysis. A modified shelving procedure, however, such as one might include in the operation for acetabuloplasty, is more effective.

Basically three different types of innominate osteotomy are described.

Pemberton Osteotomy.

This is a very good operation, although it is difficult to do well. In Dr. Pemberton's hands it has proven most successful. Such *acetabuloplasty* will effectively cover the femoral head. The only possible criticism is that it may in some cases decrease the size of the acetabulum and thereby possibly lead to pressure necrosis of the femoral head.

Salter Osteotomy.

Here the main objective is to redirect the acetabulum which in congenital dislocation is looking forward. On the contrary, it should look downward and, with the child in the standing position, the acetabulum should be redi-

rected so that it is looking at the floor. In the course of the osteotomy, every effort should be made to *keep the cut edges of the innominate bone together posteriorly* and open the osteotomy anteriorly in redirecting the acetabulum. Following surgery, the hip must be immobilized in abduction and internal rotation because the anterior soft tissue structures have been cut and will subsequently scar in. Were the hip immobilized in the Lorenz position the subsequent scarring might interfere with attempts to bring the hip down into the walking position.

Chiari Osteotomy.

This is a procedure with which we have had no experience. By comparison, it is not unlike the Salter innominate osteotomy, but one in which the distal fragment of the innominate bone is deliberately displayed medially.

Colonna Arthroplasty.

Colonna operation for congenital dislocation would seem to be primarily intended and ideally designed for the congenital dislocation in the older child where there is a marked hypoplasia of the acetabulum and a new socket has to be created. As originally advocated, it was done in two stages since the age group involved implies marked contracture of the soft tissues and shortening of the limb. The first stage consists of adductor tenotomy and hamstring stretching followed by prolonged skeletal traction until the femoral head can be pulled down opposite the level of the acetabulum. At the second stage, the hip is exposed and the capsule completely dissected away from the rim of the acetabulum. Advantage is then taken of the opportunity to ream out or gouge out a new acetabulum at its normal site and subsequently reduce the femoral head into the acetabulum after completely covering it with the excised capsule.

Femoral Osteotomy.

Osteotomy of the femur is most frequently indicated for the correction of severe anteversion. Anteversion results from instability of the dislocated femoral head and is not considered one of the primary elements in the dysplasia. Ideally, it should be possible to avoid anteversion with early diagnosis and treatment and by avoiding the forced position of internal rotation. However, it does present a problem in treatment when present and, in the older child, may have to be corrected as insufficient time and insufficient growth potential remain. The simplest femoral osteotomy is carried out in the supracondylar region of the femur after inserting a threaded wire and a Crego bow proximal to the osteotomy site. The latter is then incorporated in the spica cast to maintain the proximal femur in normal anatomical position while the distal fragment is externally rotated.

Varus osteotomy of the upper femur should seldom be necessary, as the primary abnormality is in the direction of the acetabulum. Redirection of the latter and adequate coverage of the femoral head would appear to be mechanically more desirable.

Conclusions

1. Replacing the dislocated femoral head in the acetabulum of a newborn infant is a simple and effective way of successfully treating congenital dislocation of the hip. For this reason, early diagnosis is important, and the only dependable sign of congenital dislocation in the newborn are telescoping and the Ortolani click.

2. If for lack of early diagnosis, primary treatment is delayed, the best way to reconstruct the capsular laxity of the newborn hip is adequate traction.

3. Gentle repositioning of the femoral head under general anesthesia and cutting the adductor tendons to avoid pressure necrosis is recommended.

4. Immobilization in the Lorenz position (except after surgery) will help to avoid anteversion and promote better reversal of the hypoplasia involving the anterior acetabular rim. The Lorenz position should not be forced and abduction beyond 60° is undesirable in most instances.

5. Surgical intervention is indicated if the growth potential is considered insufficient or unlikely to produce ultimate stability. This is usually not true until after 18 months of age.

6. Bilateral cases requiring surgery on both

sides do not do well. Every effort is made to treat them closed.

7. Bilateral cases over four years of age are better left alone.

Posner-Schlossman Syndrome

This syndrome is characterized by recurrent unilateral attacks of glaucoma and cyclitis. Terrien and Viel described the condition in 1929 but placed it in the general category of secondary glaucomas. Kraupa reported four similar cases in 1935. Posner and Schlossman in 1948 clearly described the syndrome and named it "glaucomatocyclitic crisis."

Included in the clinical features are a relatively white eye, an enlarged pupil, slight blurring of vision, and a very high intraocular tension. The presenting symptom is usually slight discomfort, colored halos, or blurring of vision. There is no pain. A few dilated conjunctival vessels may be seen in the affected eye. Ciliary injection is absent. Usually not more than a trace of aqueous flare is noted. Glaucoma may appear a day or two before or simultaneously with the flare. Keratic precipitates may be present at the onset or may appear a day or two later. Posterior synechiae* do not form. The intraocular tension, which remains high for a few weeks and then returns to normal, is out of proportion to the symptomatology. These episodes occur with varying frequency without resulting defects of the eye or loss of vision. Tests during symptom-free intervals are negative.

The etiology of this syndrome is not known. Posner and Schlossman suggested that it may be due to a central disturbance in the hypothalamus, superimposed on an unstable peripheral autonomic nervous system. Other writers have suggested a possible allergic factor. In differentiating this syndrome from primary glaucoma, the slit lamp is a diagnostic aid.

The syndrome follows an essentially benign course. Duration of individual attacks varies from a few hours to a few weeks. Recurrences are common. Although the condition is usually self-limited if untreated, topical cortisone has seemed beneficial in some cases. Other forms of therapy have no effect on a single episode or aid in preventing recurrent attacks.

Durham, Robert H.—Encyclopedia of Medical Syndromes
Hoeber Medical Division, Harper and Row, New York

*See Test Your Word Score, Page 45.

What Did the Patient Die of?

Let me give you an idea of the causes of death as reported in London during a typical year of the eighteenth century. There were in addition to practically all of the diseases and conditions seen today, the following causes of death: ague, bedridden, bleeding, bloody-flux, canker, cholick and twisting of the guts, evil, falling sickness, flux, French-pox, grief, griping in the guts, inflammation, itch, leprosy, lethargy, liver-grown, lunatick, mortification, planet-struck, rash, rickets, Saint Anthony's fire, scald head, scurvy, smallpox, sores and ulcers, spleen, stoppage in the stomach, teeth (which means death below age two with the exception of those deaths caused by convulsions), thrush, tympany, vapors, vomiting and looseness and worms.*

*Saul, F. William, M.D.: Pink Pills for Pale People, 1949.

Toxoplasma Gondii Infections

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THE DETECTION OF ANTITOXOPLASMA antibodies in a significant segment of the population throughout the world suggests that infections with the protozoon toxoplasma gondii are common.[1] However, toxoplasmosis as a clinical entity is rarely recognized. The majority of the infections are probably asymptomatic, and the symptomatic ones remain unrecognized, being considered as other common self-limited viral or bacterial infections. However, infection with toxoplasma gondii can produce serious and fatal disease with a great variety of clinical manifestations.

Recently new attention has been drawn to toxoplasmosis because the disease has been diagnosed with increasing frequency as an opportunistic infection in patients on immunosuppressive therapy.[2,3] Such therapy includes radiation therapy, cytotoxic chemotherapy for cancer, corticosteroid treatment and administration of immunosuppressive drugs in recipients of organ transplants, and it induces a state of increased susceptibility to infections. Even micro-organisms of low virulence and pathogenicity for the healthy individual can cause serious illness in those susceptible patients. Toxoplasma gondii appears to be among these opportunists.

Congenital Infections

An infection with toxoplasma gondii might take place during the intrauterine life, with the fetus becoming infected from the mother, who usually does not experience any clinical manifestations of her infection. This congenital infection might result in stillbirth, in birth with active disease, or in birth with the stigmata of the infection but without active progressive disease.

The newborn with active disease usually presents features resembling hemolytic disease of the newborn with anemia, jaundice, purpuric

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exanthema, hepatosplenomegaly and occasionally lymphadenopathy.[4] But any unusual undiagnosed illness of the newborn should bring toxoplasmosis into consideration. The common severe stigmata of the congenital infection are chorioretinitis, psychomotor retardation, cerebral calcifications, hydrocephaly and microcephaly.[5]

At present it is accepted that subsequent pregnancies in a woman who gave birth to a baby with congenital toxoplasmosis will not result in additional congenital infections.[1] There is no convincing evidence that a chronic endometrial toxoplasmosis is responsible for repeated spontaneous abortions.[6]

Postnatal Infections

Symptomatic toxoplasmosis in children or in adults may represent a new or primary infection, a reactivation of a previously dormant congenital, or an exacerbation of a previously latent postnatal infection. It is known that after a subclinical or clinical infection toxoplasma cysts may remain in the brain, the myocardium and other organs. Organisms released following rupture of these cysts may be the source for a recurrent infection and disease in patients with decreased resistance due to immunosuppressive therapy.

On the basis of clinical manifestations and organ system involvement, acquired symptomatic toxoplasmosis can be classified as glandular, miliary and localized types.[7]

Glandular type

The glandular type is the most common and may present as a painless lymphadenopathy without any constitutional symptoms; or it may have the clinical manifestations of infectious mononucleosis. In one study about 7% of the cases diagnosed as "glandular fever," but having a negative Paul-Bunnel reaction,* turned out to have toxoplasmosis.[8]

Miliary type

In the miliary form the protozoon is disseminated throughout the body and there are symptoms and signs from affection of many organs and systems.[7] This form presents a wide spectrum of clinical features. Fever, profuse perspirations, exanthema, conjunctivitis, headaches, nausea, vomiting, myalgias and arthralgias appear early in the course of the disease. Respiratory symptoms consisting of cough, tachypnea, dyspnea, cyanosis with signs and x-ray findings of bronchopneumonia or atypical pneumonia are observed in almost all the cases. The cardiovascular manifestations consist of fatigue, tachycardias, arrhythmias, left heart or congestive heart failure and electrocardiographic changes of conduction defects, left ventricular enlargement and myocardial injury. Lymphadenopathy and hepatosplenomegaly with jaundice may be present. The neurological and psychiatric manifestations may include hearing and vision disturbances, lethargy, psychosis, nuchal rigidity and other meningeal signs, impaired sensory perception, paresis or paralysis of extremities, abnormal reflexes, abnormalities in coordination and coma. The cerebrospinal fluid may be normal or show pleocytosis and a high protein content. Abnormalities in the electroencephalogram can be detected.

Localized type

In the localized form of the disease the infection is manifested as a disease of one organ. The localized type most probably is preceded by a subclinical or clinical generalized infection; subsequently the organisms become localized in one organ. The most frequently recognized forms of localized toxoplasmosis are the following:

Cerebral toxoplasmosis might present as an encephalomeningitis or as a space-occupying intracranial lesion or lesions with the usual focal and systemic symptoms and signs.[2]

Toxoplasmic myocarditis and pericarditis should be considered in the differential diagnosis of obscure myocardiopathies.[9] Toxoplasmic pericarditis can be a part of the constellation of the miliary infection or can be a localized infection with involvement and manifestations from the pericardium only.[10]

Pulmonary toxoplasmosis may manifest by diffuse bilateral pulmonary infiltrates associated with fever and cough and general symptoms and findings of atypical pneumonia. In patients receiving immunosuppressive therapy the consideration of pulmonary toxoplasmosis in the differential diagnosis is warranted.[11]

Toxoplasmic hepatitis, from the clinical, ser-

*See Test Your Word Score Page 45.

ological and histological point of view, is quite similar to viral hepatitis.[12] Toxoplasma organisms can be demonstrated in the liver biopsy.

Ocular toxoplasmosis is the most common localized type of toxoplasma infection, being responsible for a significant portion of cases with granulomatous uveal disease and retinochoroiditis in children and in adults.[13,14]

Diagnosis

With the described wide spectrum of clinical features and manifestations, toxoplasmosis should be considered in the newborn, in children and in adults in a great variety of clinical syndromes without evident etiologic diagnosis.

The usual blood studies do not show any characteristic or consistent changes suggestive of infection with toxoplasma gondii. The blood may be normal or show anemia, leukocytosis with neutrophilia or leukopenia, lymphocytosis with atypical lymphocytes, eosinophilia and thrombocytopenia. The urine may be normal or may demonstrate proteinuria.

Antitoxoplasma Antibodies

When this disease is suspected, determination of antitoxoplasma antibodies in the blood should be requested. The antibodies can be detected by several immunological procedures, but the most specific and sensitive procedure remains the Sabin-Feldman dye test.[1] Because of technical difficulties with this test several other immunological methods have been employed to demonstrate these antibodies. Such methods involve the complement fixation, the hemagglutination or the fluorescent antibodies technique. The technical and diagnostic advantages and disadvantages of these tests have been reviewed recently by Feldman.[1] The dye test and most of the remaining tests are performed only in a few specialized laboratories throughout the country.[15]

The detection of antibodies in the blood does not necessarily imply that the syndrome under consideration represents toxoplasmosis, because the antibodies are present in a significant portion of the population. To attribute the illness to toxoplasma infection the *antibody titer should be very high or should be rising or falling with serial determinations* done in two to four-week intervals. Nevertheless, it is well established that in certain cases of the localized form of the disease the antibody titer might be very low and not change during the course of the disease. Recently the determination of IgG and IgM antitoxoplasma antibodies has been introduced, and their determination seems to help to distinguish between antibodies due to a recent active disease and those remaining from a previous infection unrelated to the present illness.[16,17]

Biopsy

The next evidence sought to confirm the diagnosis of toxoplasmosis is the demonstration of the parasite in the vegetative free or cystic form in biopsy material. Lymph node, muscle, bone marrow and liver are the tissues usually examined. In the congenital form the cerebrospinal fluid can be examined under Wright's stain for the presence of free toxoplasmas.

The diagnosis is established and the final proof comes from isolating the micro-organisms after inoculation into mice of suspension of tissue obtained with biopsy or at autopsy. A positive inoculation experiment should be correlated with the clinical picture and serologic evidence of active disease because toxoplasma cysts have been found in organs of healthy individuals after accidental death. A negative inoculation result does not exclude toxoplasmosis, because toxoplasma of rather low virulence might not induce disease in the mouse. Blood, bone marrow, cerebrospinal fluid, muscle, lymph node, liver or any other biopsy material may be used for inoculation.

A skin test, of the delayed cellular sensitivity type, has been used for the diagnosis of toxoplasmosis. It takes several months to a year after the infection to convert to positive. Because of the poor standardization of the antigen and the frequent false negative results the skin test is not considered very useful.[1]

Treatment

To evaluate the effectiveness of any form of therapy in toxoplasma infections a large number of cases is required due to the great variability in the clinical presentation and the natural course and prognosis. At present the treatment of choice seems to be a combination of sulfonamides and pyrimethamine.

References may be secured from the author or the reprints.

Who Follow a Gleam

"A fourteen-year-old boy inspirated a scarf pin; it lodged in the right main bronchus. 'He's a dead boy,' said one of the greatest surgeons of the day. Other great surgeons said they could remove the pin but the operation, at the root of the lung, would probably result in death on the table.

"A girl slowly dying of suppurative disease of the lung. Doctor Solomon Solis-Cohen, Doctor Tello J. D'Apery, and Doctor Willis F. Manges working together discovered that the cause was a price-tag fastener that the child had inspirated while at work in a stocking factory. Doctor D. Braden Kyle invited me to go to Philadelphia to remove the foreign body by bronchoscopy at the annual meeting of the American Laryngological Association. The novelty of the procedure attracted many celebrated physicians of the day. One great surgeon looked through the port-hole in the operating-room door and passed on, remarking, 'Damned nonsense.' Less roughly expressed skepticism pervaded the audience. The case was technically one of great difficulty. The stage was set for failure, even disaster. Above all was the knowledge that the child's life hung by a thread. That day, as on hundreds of other occasions, I was grateful for 'the clear eye and the steady hand that only total abstinence from alcohol and tobacco could give,' as I expressed it years afterward in the acceptance of the Bok Award."

Who was this distinguished recipient of the Bok Award? None other than Chevalier Jackson of Western Medical School, Pittsburgh. Jackson was a doctor imbued with the spirit of discovery and exploration, who wanted to cross familiar boundaries and establish new frontiers. In addition, he loved children. It troubled him deeply to see them die after inadvertently swallowing foreign objects which lodged inextricably in their windpipes or bronchi. True, some of these objects were coughed up; but many were not. And when they were not, 98 per cent of the innocent swallowers succumbed.

Already adroit in the fields of esophagoscopy and laryngoscopy Jackson reasoned that if a precision instrument could be devised and passed through a laryngoscope it might be possible to retrieve such foreign bodies by grasping and manipulating them in such a way that they could be safely extracted. So, like other ingenious and imaginative gleam-glimpsers, he followed through; he designed just such an instrument. Thus was the bronchoscope born!

Initially he practiced long and patiently on dummies, gradually so perfecting and refining his delicate device that it would even close open safety pins before removing them. But the artificial windpipes and bronchi of his dummies were rigid passages—nothing like the soft, flexible canals in the throats and lungs of mere babes. It was unthinkable to try on small, pulsating human bodies what had worked, however successfully, on inert manikins. So what next? Cadavers! And after cadavers? Live dogs! Only after brilliant success with these warm and breathing subjects did Dr. Jackson operate on children to remove obstructions and save lives.

However, as only a single individual: one man in one place, his emergency services were inaccessible to most children in need of them; those beyond the circumference of his area of practice had no such recourse. So what to do? Teach and train others in order to disseminate his technique for wider application! This he did, supervising his trainees meticulously during the delicate procedure to ensure such clinical proficiency that no tender tissue was so much as superficially scratched. Result: the former incidence of 98 per cent mortality was reversed; 98 children out of 100 who underwent bronchoscopy survived the ordeal.

(Continued to page 28.)

Therapy for Carcinoma of the Lung

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THERE ARE SUBSTANTIAL reasons for trying new forms of therapy on patients with cancer of the lung, the most significant being that just 5 percent of the patients that develop this disease will be cured of it. The sympathies of most physicians cause them to agree with the words of Celsus, "It is better to try a double-edged remedy than none at all;" yet the wisdom of applying this precept to the patient with carcinoma of the lung is doubtful, for there is much evidence that the use of a toxic treatment ineffective against cancer is associated with an overall detrimental effect on the host.

Preoperative X-Ray Therapy

In 1960 an article appeared advocating the preoperative use of x-ray therapy to the tumor and the mediastinum of patients with cancer of the lung.[1] This proposal had much to recommend it. It might be possible (1) to damage the tumor cells sufficiently to prevent their implantation during surgery; (2) to convert an unresectable tumor to one that could be removed; or (3) to sterilize the mediastinal lymph nodes more effectively than with surgery alone. A group of 22 Veterans Administration Hospitals undertook a controlled study to test the proposition that such therapy would increase the survival rate from this disease. The study was limited to those patients that had a preoperative histological diagnosis of carcinoma. When the decision was made to operate on such a patient, one of a series of randomized envelopes was opened and, from the instructions within it, the patient was either operated upon immediately or put into the group that received preoperative irradiation. Patients in this latter group received a total of 4,000 to 4,750 rads from a cobalt source to the primary tumor and the mediastinum within 30 to 40 days. Then, following a 30-day recovery period, they underwent a thoracotomy for resection.

There was no significant difference in the immediate postoperative mortality of the two

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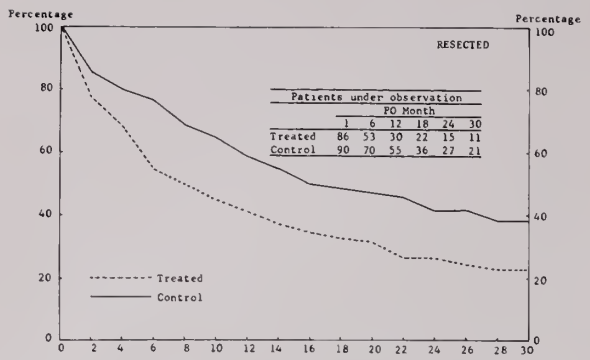


Fig. 1—Title: Preoperative X-Ray Therapy, Carcinoma of the Lung. Legend: The percentage of patients who were still alive at successive postoperative intervals. "Treated" are patients who received preoperative x-ray therapy plus a resection for cure. "Control" are patients who had only a resection for cure. The patients who died within 30 days of surgery have been removed from each group.

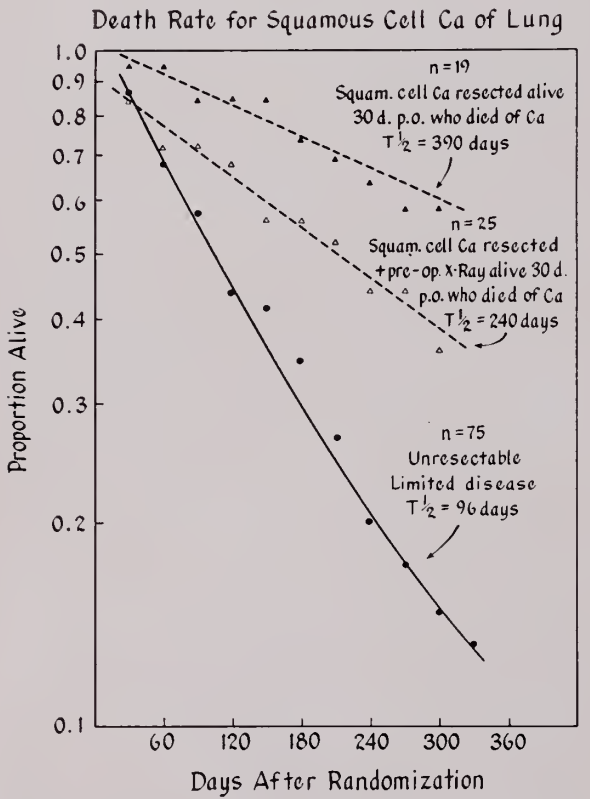


Fig. 2—Graph of the rate of death of those patients who eventually died of their cancer. The closed triangles are patients who underwent only a resection for cure. The open triangles are patients who had preoperative x-ray therapy and then a resection for cure. The closed dots are patients who had incurable disease when first seen, with the evident cancer limited to one hemithorax. T ½ is the time when 50% of the initial number of patients in the series had died.

groups; yet the late results of this study were surprising. Figure 1 is a plot of the survival curve of those patients in each group who survived the operation. Thirty-five percent of those initially put into the preoperative x-ray group were not explored because of evident metastasis or physical deterioration. Because these patients were removed from this group only, the series is weighted to favor the survival of the preoperative x-ray group. In spite of this, patients receiving preoperative x-ray therapy did significantly worse than the control group. Most of the increased mortality was due to death from cancer. This difference in mortality rate between the two groups is evident for approximately six months, after which the percent of deaths each month seems to be similar.

Several explanations for these data are possible. The additional delay of two months before surgery in the preoperative x-ray group may have permitted the cancer to metastasize in a greater number of patients. If this were so, the fraction of patients dying of cancer should be increased in this group compared to the control group; but the rate at which they die should not be different, since the severity of the disease was apparently the same in the two groups at the beginning of the study. To test this possibility, the survival of those patients with squamous cell carcinoma who underwent a resection, but later died of cancer, is shown in Figure 2 both for the group that received preoperative x-ray therapy and for the control group. These curves show a significantly increased *rate* of death for the x-ray group. From these data it would seem that the previous explanation is not true, but rather that some permanent change has occurred in the tumor or the host of the x-ray treated group.

Steroid Therapy

The result of another study on the treatment of lung cancer bears on this subject. The Veterans Administration Lung Cancer Study Group reported on a randomized double-blind study of 540 patients with incurable cancer of the lung treated with a steroid hormone, nitrogen mustard or an inactive compound.[2] The median survival of the patients who received cortisone was 56 days from entry into the study

compared to 93 days for those patients who received the inert compound. This study established in a clinical setting a phenomenon observed in mice in which cortisone therapy of a mouse with a transplanted tumor caused a markedly increased number of metastases.[3]

Cyclophosphamide Therapy

Before a particular type of therapy is used in a clinical setting, it should be demonstrated that the therapy acts more to the detriment of the cancer than to the host. Another study of the Veterans Administration Lung Cancer Group illustrates that such evidence can be obtained. The pertinent data from this study on alkylating agents is shown in Figure 3. Three courses of cyclophosphamide have prolonged the median survival of patients with unresectable small cell undifferentiated carcinoma of the lung by 75 days compared to those patients receiving an inert compound. The generation time of this tumor is approximately 45 days. The mean radius of each cell is about 4 μ and the amount of tumor present at death is approximately 1-2 kg. By assuming first, that a relationship exists between the time of death and the number of cancer cells in the host, and second, that the viable cells do not change their growth rate under therapy, it is possible to make a calculation of cell kill for this situation. From the above data, 70% of the cells originally present were killed by the three courses of cyclophosphamide.

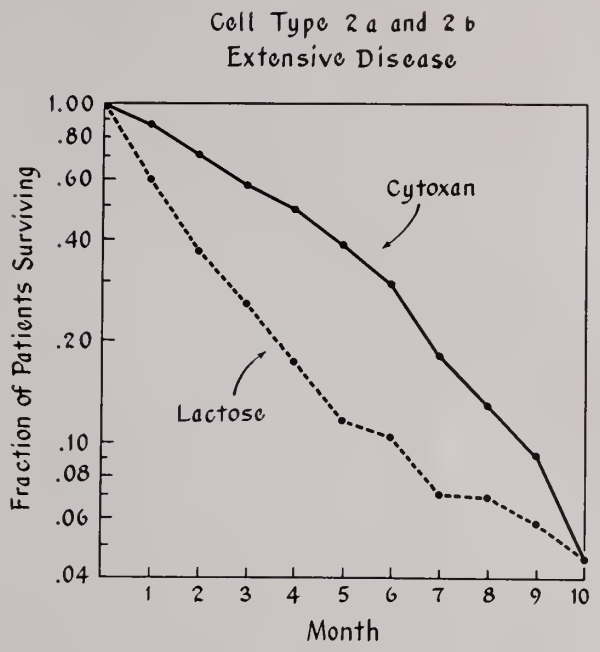


Fig. 3—Survival curves for patients with far advanced small cell undifferentiated carcinoma of the lung treated with cyclophosphamide compared to a similar group treated with an inert compound. A total of 144 patients.

Concluding Discussion

Most therapy for cancer in the past has been motivated by the supposition that cancer as a disease entity exists only within the biochemical structure of the altered cell itself, while the host is merely a passive participant, neither contributing to nor hindering the progress of the disease. Yet we do not know that the malignant process does not lie in the relationship of a slightly altered cell to the environment in which it finds itself. These studies on lung cancer at least suggest that the human patient may exert some immunological control over the tumor and that certain types of treatment may hinder this control. It might be asked why, if such immunological resistance exists, are not all the cells killed that remain after a surgical resection, since it is certainly the most favorable time? This question may be answered by assuming that all patients have the circulating cells necessary for metastasis as soon as the cancer develops and that these cells are all killed only in those patients that are cured of their cancer. Such assumptions should give all cancer chemotherapists pause in the use of very toxic and minimally effective compounds in patients that have either no proven recurrence or a cancer that has not yet shown itself to be out of control of the body defences.

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Sincerity, truth, faithfulness come into the very essence of friendship.—William Ellery Channing.

Who Follow a Gleam

(Continued from Page 24)

What contributed almost incalculably to Dr. Jackson's consummate finesse in using his instrument was his extraordinary ambidexterity. About that he says: "It is true I was not born ambidextrous; no one had a more obstinate case of right-handedness. When a boy my paternal instructions were to educate the hands, especially the left. I sought every opportunity. When a board to be sawed did not require accurate sawing to the line I did it with the left hand. At the table I kept the fork in the left hand and fed myself with it, avoiding the natural inclination to lay down the knife and fork after cutting and take up the fork in the right hand for transferring food to the mouth."

A superficial inventory of extracted items is almost breath-stopping! Buttons galore; seeds, pits, bones, shells, coins; jewelry such as charms, watches, rosaries; hardware such as nails, screws, staples, keys, even a padlock; toys such as jacks, a miniature ship, a tiny horse, a diminutive airplane; and pins ad infinitum—including open safety-pins. Most horrendous to contemplate among Dr. Jackson's illustrations is an x-ray picture of one child's lung containing a tangled conglomerate of four open safety-pins, "unsafety-pins," as Dr. Jackson called them.

The mind quails at the thought that most of the recovered objects would never again have seen the light of day had not the bronchoscope been devised. Had not Chevalier Jackson, dedicated scientist, pursued his own private gleam, the majority of these items would have been buried along with the bodies of the infants and children who became their innocent victims. Macabre thought!*

*With quotations from and acknowledgments to Chevalier Jackson: The Life of Chevalier Jackson, An Autobiography, 1938.

It's the Law

Accidental Death Benefits Payable

A policy holder was 68 years old. He fell, fracturing his tibia and fibula. He was brought to the hospital four hours later. The reduction required three and one-half hours. The policy holder was hospitalized for 50 days during which time he developed a stress ulcer with hemorrhage. He subsequently expired. The stress ulcer with hemorrhage was determined to be the cause of death. The insurance policy provided that death benefits were payable only if the death resulted directly from bodily injuries sustained from purely accidental means. The insurance company contended that the benefits were not payable because the policy holder, at the time of death, also had diabetes, liver trouble and hardening of the arteries. Competent medical evidence established the fact that the policy holder's pre-existing ailments or conditions did not contribute to his death. The court said that the accident was the direct cause of death and hence death benefits were recoverable.*

*Mutual Benefit Health & Accident Association v. Ratliff, 440 S.W.2d 119 (Tex., April 4, 1969; rehearing denied, April 25, 1969).
The Citation, 19:10, September 1, 1969.

To master one's self is the greatest mastery.—Seneca.

Application of Cryosurgery to Otolaryngology

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Cryobiology is a rapidly evolving science which concerns the methods of application and the effects of profound cold on biologic systems. Cryosurgery, a clinical extension of cryobiology, offers the promise of refining or simplifying older techniques and providing new benefits in otolaryngology and other fields of medicine.

The purpose of this report is threefold: (1) to review the methods and the effects of freezing on living tissue, (2) to explore the current clinical and investigative uses of cryosurgery in otolaryngology, and (3) to speculate on further refinements in the clinical application of cryotechniques.

Freezing Apparatus

A commercial unit (the Cooper cryosurgical unit) is available for administering cryosurgery directly or through an endoscope to any part of the body. The refrigerant in this unit is liquid nitrogen, which boils at −196 C. A triple-layered insulated cannula permits liquid nitrogen inflow, gas outflow, and vacuum insulation. This insulated cannula remains at the temperature of its environment; its tip can be cooled to any temperature (from +37 to −196 C) by setting a dial and initiating the flow of nitrogen. A series of probes is provided for specific purposes. The smallest is 2.2 mm in diameter, a size suitable for use in the middle ear and mastoid process.

A smaller cryosurgical unit (the Hill cryosurgical unit) is suitable for office use. The coolant in this model is liquid freon,† and its lowest temperature is −65 C, a factor that limits its usefulness.

A new unit (Brymill) adds versatility to cryosurgery by delivering a spray of liquid nitrogen (−196 C) directly to growths that can be exposed and isolated, and thus not freezing normal adjacent tissues. The extent of freezing

*Mayo Clinic and Mayo Foundation: Section of Otolaryngology and Rhinology.

†See Test Your Word Score Page 45.

is monitored by needle thermocouples placed in adjacent tissues.

The Effects of Freezing

The degree of coldness required to freeze human tissues varies, and the amount of damage depends on the rate of cooling and the final temperature. Decreasing temperature to −20 C will produce necrosis in all human tissues and a variety of tumors if certain conditions are not met: (1) rapid freezing, (2) a slow, spontaneous thaw until the tissue regains its original color, shape, and consistency, and (3) a second rapid freeze followed by a spontaneous thaw.

A lesion produced by this freeze-thaw-refreeze sequence is circumscribed. Its size and shape depend on the type of tissue, proximity to large vessels, and the shape and size of the cryoprobe. In homogeneous soft tissue, a spherical lesion stands out from the surrounding normal tissue. At probe temperatures between +20 and −100 C, a lesion will reach 80% of its eventual size within 30 seconds. Extended cooling, up to five minutes, will add only 20% to its size. Necrosis is gradual over one to three days, with sloughing lasting for one to two weeks. A slough is as sharply demarcated from living tissue as the original lesion; it is generally free of suppuration; and it evokes minimal surrounding inflammation. Histologically, the frozen area resembles an ischemic infarct.

Cryonecrosis is the final result of several insults to the cell structure: 1. Freezing dehydrates the tissue and produces toxic concentrations of electrolytes. This abnormal electrolytic environment denatures the lipid-protein complexes of the cell membrane, and the cell bursts. 2. Actual crystal formation within the cell and extracellular space causes further damage to the membrane. 3. So-called thermal shock is a separate effect of the rapid change of temperature. This shock injures the cell in a distinct manner and may explain why rapid freezing is more damaging than slow cooling to the same low temperature. The rapid freeze may initiate an antibody response against the tissue that was frozen.

Clinical Application

A new method must offer an advantage over contemporary forms of treatment to justify its clinical use. In this respect, cryosurgery seems promising in the field of otolaryngology. Because of rapid intracapillary thrombosis in the frozen area, the striking feature of all clinical investigations has been the absence of significant bleeding during or after the procedure. Large arteries and veins resist cryonecrosis even when deliberately frozen, a phenomenon which explains the absence of late bleeding.

Pain relief

Peripheral nerves and nerve endings seem particularly susceptible to rapid freezing, a property which is exploited in cryosurgical palliation of painful neoplasms.[1,2]

Meniere's disease

Cryosurgical techniques have been adopted by the otologist in his quest for a predictable treatment of Meniere's disease. Two approaches have been tried: (1) the selective destruction of the vestibular neuroepithelium, and (2) a drainage procedure.

Experimentally in monkeys and clinically in certain patients with Meniere's disease, Wolfson's group[3] has pioneered the selective destructive procedure. Their goal has been to relieve vestibular symptoms and preserve hearing. In monkeys conditioned to sound, careful cryotherapy over the thinned horizontal semicircular canal consistently eliminated caloric response without changing hearing or functions of the facial nerve. Clinical trials were less promising. Fourteen of 15 patients lost their caloric response in the treated ear, but six of these experienced further vertigo. Three patients lost additional hearing, and only four of the entire group were free of vertigo with stable or improved hearing. More recent clinical trials with refinement of technique have been more promising.

Another approach to the treatment of Meniere's disease has been advanced by House.[4] The object of his procedure is to produce a shunt between the otic and perotic labyrinth without opening the perilymphatic space. The technique, called the "cryogenic otic-perotic shunt," uses a tympanotomy approach (as in stapes procedures) and involves cooling over the thin promontory. The purposes are: (1) to

equalize pressure between the cochlear duct and the perilymphatic scala to prevent vertigo, (2) to eliminate the unpleasant pressure sensation of Meniere's disease, and (3) to preserve or improve hearing. House[4] expressed the opinion that the cold temperature penetrates the cochlea and vestibule of the inner ear and destroys or effectively damages the basilar membrane, Reisner's membrane, and possibly the wall of the saccule. In the 69 patients so treated, 70% of the procedures were considered successful in that vestibular symptoms were eliminated and hearing was improved or at least did not deteriorate further. When observed six months after operation, the patients who had improved initially showed no evidence of symptoms. House considers this a safe and simple procedure. He stated that he planned to use it in treating patients with early, uncompensated Meniere's disease who do not respond quickly to medical management but who have not experienced permanent loss of hearing. Little has been heard of this technique.

Surgery of the nose

Three situations have attracted the rhinologist: (1) transnasal pituitary ablation, (2) control of severe epistaxis, and (3) nasal polypectomy. The value of pituitary destruction and palliation of some endocrine-dependent metastasis from malignant lesions has been established. Most patients with bone pain from metastatic carcinoma of the breast are candidates for this form of therapy. The transseptal approach to the pituitary glands is particularly adaptable to cryosurgical techniques, and several reports indicate that cryonecrosis totally destroys the glands. Rand and co-workers,[5] Griffin and associates,[6] and Bleasel and Lazarus[7] have used different factors of time and temperature for performing transnasal cryogenic hypophysectomy and have been encouraged by successful ablation and relief of pain in patients with metastatic disease. Also, they have noted clinical and chemical evidence of ablation in patients with primary pituitary neoplasms.

Bluestone[8] reported significant success with the cryoprobe in treating severe epistaxis, particularly that associated with hereditary hemorrhagic telangiectasis. Painless cryonecrosis of nasal polyps has been reported by von Leden and Rand.[9] Although this technique has slight practical advantage over conventional methods, its success illustrates the versatility of the cryoapparatus.

Tonsillectomy

Cryonecrosis is an accepted method for destroying tonsillar tissue. Volunteers and patients with blood dyscrasias have been pleased with the absence of discomfort, the absence of surgical and delayed hemorrhaging, and the fact that they are permitted to leave the hospital on the day of the operation. Hill,[10] using the freon unit, has performed tonsillectomies by cryosurgery in his office. Experience has established cryosurgery as a practical alternative to excisional surgery for total destruction of diseased tonsils.[9,10]

Tumors of the head and neck

Cryotechniques provide additional opportunities for managing malignant and benign tumors of the head and neck. Cryosurgery should be considered (1) as an adjunct to excisional surgery of vascular neoplasms, (2) as a primary destructive agent, and (3) as a palliative tool for advanced malignant lesions.

Freezing serves as a valuable adjunct to the excision of vascular tumors. Glomus jugulare, nasopharyngeal angiofibromas, and extensive hemangiomas are neoplasms in which the hemostatic properties of cold are of obvious value. Nevertheless, the experience of Smith and associates[11] with excision of angiofibroma emphasizes the fact that freezing is only a subordinate procedure to decrease hemorrhaging. The usual precautions of having blood available for transfusion, of planning several intravenous routes, and of wide exposure are essential for the safe performance of this type of operation. To obtain maximal benefits, large tumors must be frozen as close to their attachment as possible before removal.

The use of cryonecrosis as the primary agent in tumor destruction is almost an unexplored field. The experience of Gage and associates[12] with selected lesions of the lip and of the oral cavity should stimulate further investigation. By repeatedly applying the cryoprobe, five large malignant tumors were destroyed in elderly patients.

Palliative cryosurgery

The suitability of cryonecrosis for palliation of painful, bulky, advanced malignant lesions is most welcome. The features of relative freedom from bleeding plus the vulnerability of peripheral nerves and nerve endings to freezing make this procedure an attractive alternative to other methods. Hill[10] has reported relief of pain, decrease in bulk, and return of swallowing after applying the endoscopic cryoprobe to large, inoperable, postirradiated laryngopharyngeal tumors. The value of cryosurgery for palliation of bulky metastasis of the neck, of stomal recurrence of laryngeal carcinoma, and of hypopharyngeal, esophageal, and paranasal sinus carcinoma is being studied.

A few attempts to freeze benign laryngeal growths have been reported. Von Leden and Rand's[9] work with granuloma and contact ulcer is encouraging. Also, their cryosurgical endeavors to control papilloma of the larynx in juvenile patients are significant.

Speculations for Future Use

With cryosurgical units commercially available, the major engineering problem to provide satisfactory equipment appears solved. A more versatile selection of probes of various sizes and shapes should follow as the needs become known to the instrument designers. For the cryosurgical technique to reach a stage of predictability, factors of time and temperature must be standardized. One can envision treatment charts which incorporate the various types of tissue, the vascularity of the tissues, the nature of the surrounding tissues, the proximity of large vessels, and the therapeutic objective. Such criteria will eliminate guesswork and overdependence on clinical judgment.

The clinical application of cryosurgery seems limited only by the imagination of investigators. The combined capacity of cryonecrosis, antineoplastic drugs, and irradiation for destroying malignant tumors remains unexplored. As a definitive therapeutic agent in the early management of carcinoma, especially early malignant lesions of the vocal cords, cryonecrosis offers potentiality. Cryosurgery is evolving as a useful method in the field of otolaryngology.

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Posted conspicuously at the entrance of a midwestern town is the following sign:

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No brain is stronger than its weakest think.—Thomas L. Masson.



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A smoll fraction of the harmanol agents in orol cantraceptive pills has been identified in the milk af mothers receiving these drugs. The long-ronge effect on the nursing infont connat be determined ot this time.

Indication—Oral contraceptian.

Contraindications—Thrombophlebitis, thromboembolic disorders, cerebral apoplexy or a past history of these canditians, markedly impaired liver functian, known or suspected carcinama of the breast, known or suspected estrogen-dependent neoplasia, undiognosed obnormal genital bleeding.

Warnings—Watch far the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, retinal thrambosis); if present or suspected discontinue the drug immediotely.

British studies reported in April 1968[1,2] estimate there is a seven- to tenfald increase in mortality and morbidity due to thromboembolic diseases in women taking oral contraceptives. In these controlled retrospective studies, invalving 36 reported deaths ond 58 haspitalizations due ta "idiopathic" thromboembolism, statistical evaluation indicated that the differences observed between users and non-users were highly significant. The conclusians reached in the studies are summarized in the toble below:

Camparisan of Mortality and Haspitalizatian Rates Due to Thrombaembolic Disease in Users and Non-Users af Oral Cantraceptives in Britain.

Categary	Mortality Rates		Haspitalizatian Rates (Morbidity)
	Age 20-34	Age 35-44	Age 20-44
Users of Oral Contraceptives	1.5/100,000	3.9/100,000	47/100,000
Non-Users	0.2/100,000	0.5/100,000	5/100,000

No comparable studies are yet available in the United States. The British data, especially as they indicate the magnitude of the increased risk to the individual patient, cannot be applied directly to women in other countries in which the incidences of spontaneously occurring thromboembolic disease may differ.

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or sudden onset of proptosis, diplopia or migraine. Withdraw medication if papilledema or retinal vascular lesions are found.

Since the safety of Ovulen in pregnancy has not been demonstrated, it is recommended that pregnancy be ruled out for any patient who has missed two consecutive periods before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule the possibility of pregnancy should be considered at the first missed period.

A small fraction of the hormone agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The lang-range effect an the nursing infant cannat be determined at this time.



Precautions—Pretreatment physical examination should include special reference to the breasts and pelvic organs, and a Papanicolaou smear.

Endocrine and possibly liver function tests may be affected by Ovulen. Therefore, it is recommended that such tests if abnormal be repeated after the drug has been withdrawn for two months.

Pre-existing uterine fibromyomas may increase in size under the influence of progestogen-estrogen preparations.

Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation.

In breakthrough bleeding, and all irregular vaginal bleeding, consider nonfunctional causes. Adequate diagnostic measures are indicated in undiagnosed vaginal bleeding.

Carefully observe patients with a history of psychic depression and discontinue the drug if severe depression recurs.

Any possible influence of prolonged Ovulen therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study.

A decrease in glucose tolerance has occurred in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be observed carefully while receiving Ovulen.

Because of the effects of estrogens on epiphyseal closure Ovulen should be used judiciously in young patients in whom bone growth is not complete.

The age of the patient constitutes no absolute limiting factor, although Ovulen therapy may mask the onset of the climacteric.

The pathologist should be informed of Ovulen therapy when relevant specimens are submitted.

Adverse Reactions—A statistically significant association has been shown between use of oral contraceptives and the following serious adverse reactions: thrombophlebitis, pulmonary embolism.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: cerebrovascular accidents, neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptams (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, breast changes (tenderness, enlargement, secretion), change in weight, changes in cervical erosion and cervical secretions, suppression of lactation when given immediately post partum, cholestatic jaundice, migraine, allergic rash, rise in blood pressure in susceptible individuals, mental depression.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: anovulation post treatment, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme and nodosum, hemorrhagic eruption, itching. The following laboratory results may be altered by oral contraceptives: hepatic function: increased sulfobromophthalein and other tests; coagulation tests: increase in prothrombin, Factors VII, VIII, IX and X; thyroid function: increase in PBI and butanol extractable protein bound iodine, and decrease in T^3 uptake values; metyrapone test; pregnanediol determination.

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Editorials

Anastomosis of Ascending Aorta and Right Pulmonary Artery*

Doctors B. R. Dooley, R. G. Armstrong, and W. Stanford have reviewed their experience with a relatively new and increasingly used type of systemic-to-pulmonary artery shunt, the ascending aorta-right pulmonary artery anastomosis. First described by Waterston[1] and later widely discussed by Fuller,[2] Edwards and associates,[3] and Cooley and Hallman,[4] this procedure has proved useful in the treatment of cyanotic heart disease, particularly for infants less than one year old. The article emphasizes some of the advantages of this anastomosis: It is relatively easy to construct; it can always be performed through a right thoracotomy regardless of the side of the aortic arch; it does not require an extensive dissection of the mediastinum (as do the Potts and Blalock procedures), and it is relatively easy to repair at the time of total correction of the cardiac defects.

This procedure is also useful in some instances in which emergency surgery must be undertaken on a cyanotic infant before a complete or correct diagnosis can be made. For example, a presumptive diagnosis of severe tetralogy of Fallot or pulmonary artery atresia may be made before operation, but at the time of exploration, transposition of the great vessels may be encountered. With this type of incision, however, an atrial septal defect may be created (Blalock-Hanlon procedure) without difficulty. The converse can also happen, namely, operation for transposition of the great vessels revealing pulmonary artery atresia. In this situation, the incision easily permits the construction of a Waterston type of systemic-pulmonary shunt.

Therefore, it is not as critical to obtain a preoperative diagnosis before emergency surgery on the critically ill and deteriorating cyanotic infant, if the diagnostic choice is between the two most common malformations—tetralogy of Fallot (or pulmonary artery atresia) or transposition of the great vessels.

Occasionally, the patient with an inoperable cyanotic heart lesion outgrows the Blalock anastomosis. The Waterston procedure provides a simple solution to what might otherwise be a difficult problem in constructing a second (or third) systemic-to-pulmonary artery shunt.

The authors carefully outline the hazards of this type of anastomosis, the chief one being the production of heart failure from a shunt that is too large. As with the Potts anastomosis, the size of the shunt is very critical, and the usual tendency is for the anastomosis to be too large or for its size to increase disproportionately as the patient grows. This leads early to heart failure and later to pulmonary vascu-

*Dooley, B. R., Armstrong, R. G., and Stanford, W.: Artery Shunt for Cyanotic Heart Disease—Intrapericardial Ascending Aorta-Right Pulmonary Artery Anastomosis. Minnesota Med 52:409, 1969.

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lar obstructive disease and pulmonary hypertension, all of which render the patient inoperable for total correction. Mild degrees of heart failure can be controlled medically, but, as the authors indicate, uncontrolled heart failure should be managed by reoperation and narrowing of the shunt.

As with any small vascular anastomosis, thrombosis may occur. This is much less likely to complicate a Waterston than a Blalock anastomosis (which may be compromised by a tiny subclavian artery). When thrombosis occurs, it can readily be corrected by reoperation, as illustrated by one of the authors' cases.

An unanticipated problem, as mentioned by the authors, is the production of stenosis of the right pulmonary artery during closure of the defect. Hopefully, this can be managed by an awareness of the possibility of producing stenosis and by increased care in closure.

There is considerable discussion as to whether this type of anastomosis is desirable in patients who are older than one year. Because physiologically this anastomosis is similar to a Potts operation, in which inoperable pulmonary vascular disease develops in at least 15% of the patients, a Blalock anastomosis may be preferable in these patients even though this requires a somewhat longer dissection and operation. Experience at our clinic indicates that the presence of a previous Blalock shunt does not increase the risk of total correction of tetralogy of Fallot, although it does add to the technical difficulty and length of the procedure.

The authors describe the use of this shunt for four patients with tricuspid atresia. The addition of balloon septostomy, in order to enlarge the atrial septal defect, may improve the chance for survival of patients with this severe anomaly, as suggested by Waldhausen.[5]

Systemic-to-pulmonary artery shunts remain useful operations in the initial treatment of tetralogy of Fallot and other cyanotic cardiac anomalies, and they can be life-saving when performed expeditiously in the critically ill infant. My colleagues and I would concur with the authors that the ascending aorta-right pulmonary artery anastomosis represents a significant advance in the development of systemic-to-pulmonary artery shunts, particulary for newborn patients and those less than one year old.

Gordon K. Danielson, M.D.
Rochester, Minnesota

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5. Waldhausen, J. A.: Discussion. Arch Surg (Chicago) 95:715, 1967.

Diagnosis of Animal Parasites

THE PAPER BY Williams, Nelson and Zymet* on trichinosis once again emphasizes the need for the physician to be alert in the recognition of parasitic infections which, though not among the major health hazards in Minnesota, must be recognized when they occur. Besides Trichinella and the ubiquitous pinworm *(Enterobius)*, *Diphyllobothrium latum*, *Taenia saginata*, *Strongyloides stercoralis*, *Ascaris lumbricoides*, *Giardia lamblia*, *Entamoeba histolytica*, and certain maggots, especially *Wohlfahrtia* in infants, have been acquired in Minnesota.

The problem of considering and recognizing the parasites that may occur in foreign students, tourists, veterans, and others who have been in other countries is much more formidable. With the memory of World War II cases and the current interest in returnees from Viet Nam, the possibility of malaria in a returned traveler is probably considered frequently.

*Williams, L. P., Jr., Nelson, C. B. and Zymet, C. L.: Trichinosis Outbreak in Minnesota and Iowa. Minnesota Med. 52:1153, 1969.

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Less well-known infections that have appeared in Minnesota in recent years include leishmaniasis,* trypanosomiasis, coccidiosis, schistosomiasis, clonorchiasis, loiasis and myiasis caused by the human bot fly.

The seemingly impossible task of thinking of all of these and many more possibilities is simplified if the physician remembers that many of them have limited and precise geographic distributions. A detailed knowledge of the places where a patient has been often can suggest a particular parasite or can enable the physician to rule out certain ones.

Any patient who has been out of the country should therefore be asked where he has been, not just the general part of the world but the particular countries and places. The parasitology text books all give some geographic information, but a most helpful book is "Exotic Diseases in Practice" by Brian Maegraith (American Elsevier, 1965). Besides giving brief descriptions and diagnostic suggestions for exotic diseases (not only those caused by animal parasites) it lists such diseases by world areas and countries.

Once the crucial step of thinking of the possible parasites has been made, the diagnostician can enlist the aid of the State Department of Health or the National Communicable Disease Center for technical assistance, as Williams, Nelson and Zymet did.

Franklin G. Wallace, Ph.D.†
Minneapolis, Minnesota

†Professor of Zoology, University of Minnesota.
*See Test Your Word Score, Page 45.

Malnutrition*

THE DERIVATION of "malnutrition" is based on the Latin *mal*, which means evil or bad. Thus, one can justify the use of the term "malnutrition" to describe impairment of health resulting from the consumption of either excessive amounts or certain varieties of food, even though malnutrition traditionally is associated with dietary deficiencies. Hence the obese person and the person who has coronary artery disease as a result of indulgence in excessive quantities of foods, rich in cholesterol and saturated fats, may be considered malnourished.

Keys has reviewed the relationship between serum cholesterol levels and coronary artery disease, as well as the means available to lessen the frequency of clinical coronary artery disease. He emphasizes that any measure employed will have to be continued rigorously and long, because it is only by maintaining serum cholesterol levels at a substantially lower level for years that one can expect benefit. One piece of good news is that the fat in chocolate (mostly stearic acid) is no longer considered to have a significant cholesterol-raising effect.

Keys' primary recommendation is that we attempt to revise the dietary habits of the general population. Although difficult, this is not impossible. And if palatable substitutes for eggs, ice cream, and other tasty "staples" of our current diet can be found, the cure will not be unpleasant. Perhaps in the future the Minnesota dairy farmer will depend more and more on the protein content of the milk he produces, and regard the butter fat as largely waste, as far as human consumption is concerned. Certainly margarine seems a widely accepted substitute for butter. And more and more persons enjoy skimmed milk rather than whole milk. Pediatricians' advice regarding feeding problems in childhood will have longer-term effects in the form of establishing food preferences and habits.

Alcohol appears to aggravate some forms of hyperlipidemia, and some physicians would advise restricting alcohol consumption for the person who wants maximal mileage from his coronaries.

Undoubtedly the views and recommendations expressed by Keys simplify a complex problem. The classification of the various states of hyperlipidemia[1] is notable for its complexity and continuing evolution. These states presumably are genetic in origin, but their manifestations can be modified by dietary manipulation. Keys' discussion aims broadly at the general

*Keys, Ancel: A Practical, Palatable Way of Eating. Minnesota Med. 52:1259, 1969.

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population rather than at those persons with unusual susceptibility to hyperlipidemia. His recommendations, if carried out, might correct the most common serious form of malnutrition in our country, and perhaps extend life expectancy and improve health more than any other medical measure now available.

Clifford F. Gastineau, M.D.
Rochester, Minnesota

Reference

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Cough Syncope

ALTHOUGH RECOGNIZED and described over ninety years ago, cough syncope remains a fascinating and incompletely understood clinical entity. This syndrome, occurring almost exclusively in the obese, stocky, muscular middle-aged male smoker with chronic bronchitis or emphysema (who is said to enjoy good meals and beverages), is characterized by a vigorous paroxysm of non-productive coughing followed in three to five seconds by giddiness and sudden unconsciousness lasting about ten seconds. The unconsciousness, which may be accompanied by clonic movements, is seldom fatal. When recovery occurs about ten seconds later, the patient is amnesic, but has no confusion as in the postictal* state. The syndrome may occur in the supine, sitting, or standing position, and usually can be reproduced again in the same individual. Such patients may say they cannot control the coughing paroxysm once it has begun.

The paper in the October issue of MINNESOTA MEDICINE by Skolnick and Dines† confirms the general features of this syndrome and points out that many physiological changes occur during the coughing paroxysm. A few general points about this syndrome should be emphasized. Coughing in normal subjects and in patients with chronic bronchitis or emphysema causes increased intrathoracic pressures of from 50 to 150 mm. of mercury, while coughing in patients with cough syncope produces peak pressures of from 200 to 300 mm. of mercury.[1,2] This increased intrathoracic pressure is transmitted to the intra-abdominal and the intracranial spaces as well. Pressures of this magnitude may act in three ways to cause syncope. First, the cough acts physiologically like a strong Valsalva maneuver, causing decreased venous filling of the atria with consequent decreased blood pressure and stroke volume leading to decreased cerebral perfusion. Second, the increased intrathoracic, intra-abdominal, and intracranial pressures produce a "squeezing" of venous and arterial blood out of the respective cavities, leading again to decreased cerebral perfusion and hypoxia.[3] Third, the sudden increased intracranial pressure is thought to act much like a cerebral concussion in causing subsequent unconsciousness.[4] It is interesting that cardiac arrhythmias have not been described as a common feature of this syndrome.

It is unlikely that any single mechanism is responsible for the syncope that is seen with coughing, as none completely explains all the features of the syndrome. For example, if decreased blood flow to the brain is the sole cause, why does the syncope come on so rapidly (three to five seconds) after coughing? Also, if venous "squeeze" is the important mechanism, why can syncope be produced in these patients when they have a G suit on?[4] Obviously, with the presently available physiological data, answers to these questions are not readily available, and we are led to postulate, as Skolnick and Dines suggest in their summary, that multiple physiologic mechanisms are probably involved in the production of cough syncope, and that these may vary from one patient to another.

Wilfred A. Corson, M.D.
St. Louis Park, Minnesota

*See Test Your Word Score Page 45.

†Skolnick, J. L. and Dines, D. E.: Tussive Syncope. Minnesota Med 52:1609, 1969.
References may be secured from the author.

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Where Will It End?

THE TIME-WORN and flimsy excuse for liberalizing rules of evidence and new methods for proving malpractice is the "conspiracy of silence." This seems to mean that if a physician reviews the evidence and does not find a departure from the standard of care and cannot therefore testify that malpractice existed, he is a "conspirator" against the patient who is praying for an award.

There has been no dearth of suits against doctors in recent years, and every case has produced physicians who testified in behalf of the plaintiff. Where is the conspiracy of silence?

Many professional liability carriers have withdrawn from the malpractice field. A doctor makes thousands of life and death decisions in the course of his professional lifetime, yet if he makes one wrong decision, he may lose all he has worked a lifetime to acquire—and be unable to obtain liability insurance thereafter.

The physician shortage becomes more and more acute. Even so there is talk of re-licensing examinations at three-year intervals and the training of sub-doctors.

Will the day come when a doctor will be forced to say, "I'd like to help you, but I just can't take the risk!"*

Editor's Note: Can you imagine the possibility of licensing a sub-doctor and refusing to renew a license for a qualified physician who might, on the basis of a few questions, fail his internal examination? Here is where I would like to say that many of our senior peers have forgotten more than a sub-doctor might ever learn. E.R.

*Excerpts from Paul B. Jarrett, M.D., Arizona Medicine, July 1969.

Test Your Word Score

Litholapaxy—*the crushing of a calculus in the bladder, followed by the washing out of the fragments* (page 12).

Synechiae—*adhesion of parts* (page 20).

Paul-Bunnel reaction—*the inactivated serum of patients with infectious mononucleosis will agglutinate sheep red corpuscles* (page 22).

Freon—*a combination of hydrocarbons having one or more fluorine atoms in the molecule, sometimes used as a refrigerant* (page 29).

Leishmaniasis—*a disease probably transmitted by the sandfly and characterized by ulceration of the mucous membranes of the nose and throat* (page 41).

Postictal—*following a seizure* (page 43).

Haversian system—*a series of concentric lamellae arranged about a central canal in compact bone* (page 51).

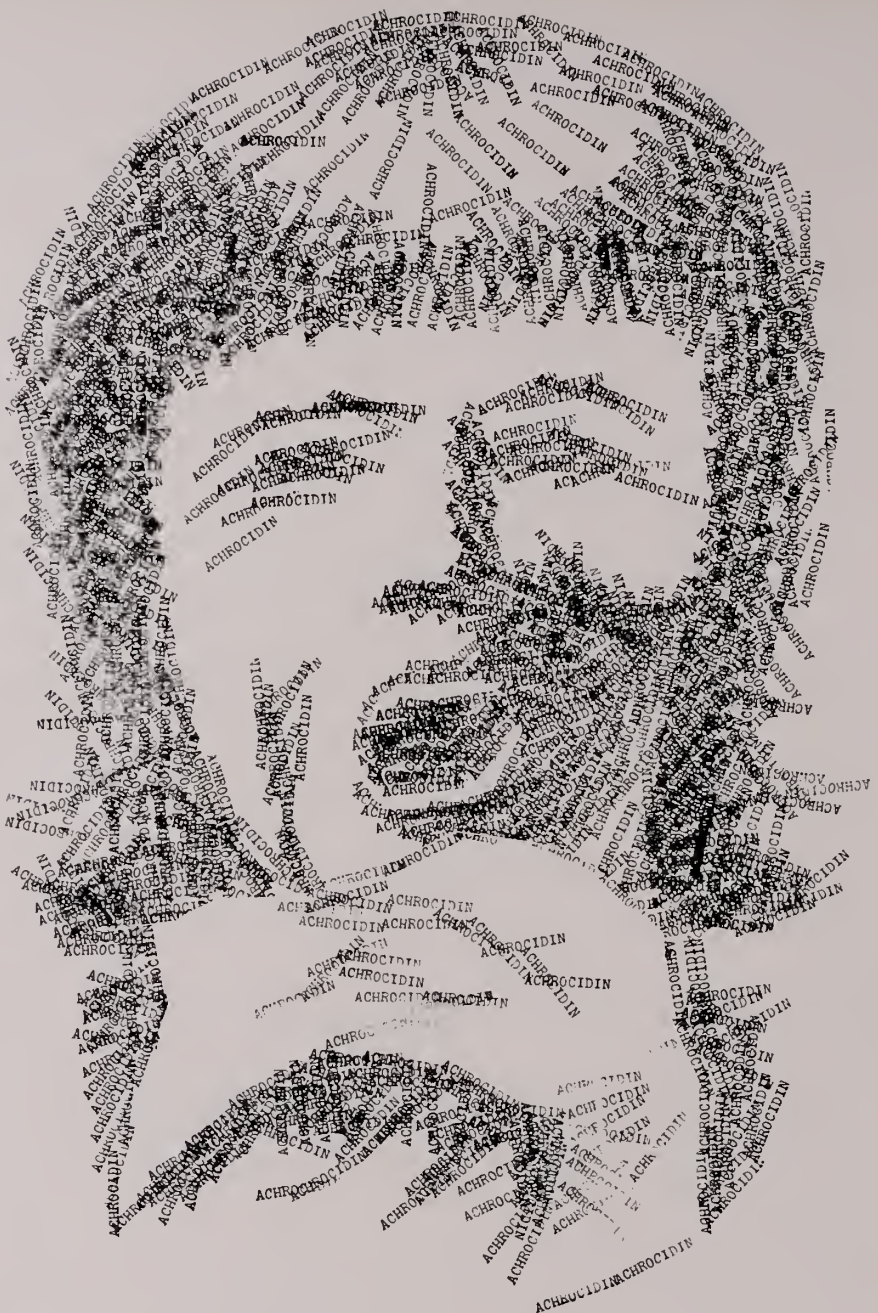
Ontogeny—*developmental history of the organism* (page 78).

Perleche—*a form of oral moniliasis in children* (page 79).

Hydranencephaly—*complete or almost complete absence of the cerebral hemispheres, their space being occupied by cerebrospinal fluid* (page 81).

Torulosis—*a Cryptococcus infection that has a predilection for the brain and meninges* (page 86).

Triage—*the sorting out and classifying of the wounded brought to a field hospital* (page 94).



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Adverse Reactions: *Gastrointestinal*—anorexia, nausea, vomiting, diarrhea, stomatitis, glossitis, enterocolitis, pruritus ani. *Skin*—maculopapular and erythematous rashes; exfoliative dermatitis; photosensitivity; onycholysis, nail discoloration. *Kidney*—dose-related rise in BUN. *Hypersensitivity reactions*—urticaria, angioneurotic edema, anaphylaxis. *Intracranial*—bulging fontanels in young infants. *Teeth*—yellow-brown staining; enamel hypoplasia. *Blood*—anemia, thrombocytopenic purpura, neutropenia, eosinophilia. *Liver*—cholestasis at high dosage.

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The Editor's Soliloquy

Ruminations at the Meeting

To keep abreast of the times your Editor does occasionally attend a medical meeting. He takes notes, talks to the doctors, solicits a manuscript or two, then returns home and goes to work.

To make you privy to my thoughts re MINNESOTA MEDICINE, and incidentally other medical journals, here are a few of my casual notes; to be developed later.

Doodles: might they not be even more revelatory than stereotyped inkblots? Perhaps we could gain diagnostic insight into an elusive patient by studying his extemporaneous doodles; couldn't they be more challenging, besides being less frustrating than the psychedelic imaginative reactions to the Rorschach test? But now I'm getting off the beam, the speaker was offering a few titles for feature headings.

Table of Contents: if there is one on the cover, eliminate the minutiae, as they can irritate both the eye and the mind; feature only the main articles. Don't hide it in the ads, though, as the reader might get discouraged and toss it.

Headings: have plenty, for they are valuable traffic signs.

Specifics: watch out for them; they can tie you up pretty close.

Rebuttals: such a section might be as electrifying as a tomcat fight—with partisanship crescendoing to top pitch on some issues. However, such feline confrontations should never get out of hand but always stop short of mayhem, their gravity lightened by a moiety of bravado rather than recrimination.

Breathers: such as a Clergy-M.D. Breather. Priests, ministers, rabbis on the one hand and doctors on the other hand fall into similar categories since they all deal with birth, death, and the unpredictable interval between. Death? that might be certain but the date and hour are unpredictable too! Enjoy life, you'll soon be dead. Wow!

X-ray of the Month, Picture of the Month: Electrocardiogram of the Month, etc. I personally don't know a T-wave from a QRST wave, but I might learn to distinguish. Deploring triteness we still endorse the early Chinese aphorism that one picture can be worth—was it a thousand words—I matched my Arabic letters of a sentence with the pictorial words of a young Chinese doctor. He won, and besides all the Orientals can read it even though they can't speak it. Seems funny, doesn't it?

Letters to the Editor: no! That phraseology sounds dull and lacks inducement. We call ours You May Be Right: In any dialectic, antithesis leads to final synthesis; rational opinions tend to converge and accommodate rather than polarize.

Journalese: should we perhaps drift away from traditional medical journalism—the hitherto-prevailing Morris Fishbein type: thoroughly professional in its compositional integrity and its reliance on the earnest reader's capacity and fortitude to follow through? Should we even be so *laissez-faire* as to incorporate levity into our tone or even expletives into our diction, the degree of each to depend on whether the spoken or written word is under consideration?—"I don't give a rancid d—!" Now there's a startling expression—quite acceptable when emitted by a vehement speaker but much too heterodox in a published monograph. Under the circumstances, however, it jerked me to attention, as it surely was calculated to do. Which leads me to wonder: could we profit from such occasional one-up-manship in a journal?

Well there, those are my notes! There were many more, but I am ruminating myself out of space. Incidentally, I had fun too: brought my wife along. I always do; she's one of my assets, you know!

Carl O. Rice, M.D.
Editor-in-Chief

Samuel Pepys and His Stone

Mr. Pepys suffered from stone in the bladder before he began to keep a diary.

Cutting for the stone was one of the earliest surgical operations. In ancient days it was first done in India, and the glad news that stones could be successfully removed from the living body filtered through to the Greeks some centuries before Christ.

By Pepys' time Marianus Sanctus had lived—yes, so greatly was he venerated that they called him "Sanctus." He it was, in Italy in 1524, who invented the apparatus major, which made the operation a little less barbarous than that of the Greeks. This God-sent apparatus consisted mainly of a grooved staff to be shoved into the bladder and a series of forceps. You cut on to the staff as the first step of the operation; it was believed that if you cut in the middle line in the raphe the wound would never heal, owing to the callosity of the part; moreover, if you carried your incision too far back you would cause fatal haemorrhage from the inferior haemorrhoidal veins. Having, then, made your incision well to the right or left, you exposed the urethra, made a good big hole in that pipe, and inserted a fine able pair of tongs, with which you seized hold of the stone and crushed it if you could, pulling it out in bits; or if the stone were hard, and you had preternaturally long fingers, you might even get it out on a finger-tip. It was always considered the mark of a wise surgeon to carry a spare stone with him in his waist-coat pocket, so that the patient might at least have a product of the chase to see if the surgeon should find his normal efforts unrewarded.

This would be the operation that was performed on Mr. Pepys. One unpleasant result was the fact that whenever he crossed his legs carelessly he became afflicted with a mild epididmyitis—he described it much less politely himself, doubtless in wrath. His little failing in this respect must have been a source of innocent merriment to the many friends who were in the secret.

When he died, an old man, in 1703, they performed a post-mortem examination on his body, suspecting that his kidneys were at fault, and in the left kidney found a nest of no less than seven stones, which must have been silently growing in the calyces for unnumbered years.*

*C. MacLaurin: Post Mortems of Mere Mortals, 1925.

Emerging Patterns of Medical Care and Practice

The central plot of this story is, in a sense, the central plot of all social history—man's struggle to rearrange his social organization and institutions, to keep pace with his accumulating knowledge, changing needs and altered environment. As in all phases of human enterprise, realistic available choices are limited, but they are not absent. Freedom to avoid the basic fact of change does not exist—either biologically or socially—but the character and adequacy of the adjustment to change is, in varying limits, subject to human decision. It is, of course, possible for a society or a group to attempt to resist adjustments altogether—either actively or by inertia—but the price is to be run over.*

*H. M. Somers and A. R. Somers in Richard Magraw: Ferment in Medicine, 1966.

Man

Fat men have to be good-natured, because they can't fight or run.—Anon.

Old Doc Hess says: It's better to have a good bad habit than a bad good habit.



Curbstone Consultation

Pulmonary Alveolar Proteinosis

QUESTION: I suspect a patient under my care of having pulmonary alveolar proteinosis. Is there any effective treatment for this condition or is it an invariably fatal disease? Can the diagnosis be established short of resorting to lung biopsy?

ANSWER: The etiology of this disease is uncertain, although theories have been advanced proposing a possible interaction of surfactant and plasma leading to the deposition of the intra-alveolar material found in this condition.

A sputum found to have an acid pH should heighten the clinician's suspicion as to the existence of this disease entity in a patient suspect. Chest x-rays which show a characteristic "butterfly" distribution of the infiltrate or mottling that is radiographically demonstrated without evidence of interstitial involvement can be very helpful diagnostically. Vidone et al.[1] have devised a method for examining the sputum to identify the characteristic material found in pulmonary alveolar proteinosis. Using several stains they found a staining pattern which they feel is characteristic in this condition and, in the group of patients they studied, found only one false-positive result. Lung biopsy, however, remains the only way one may make a definitive diagnosis of this disease. Lung tissue involved by this disease process will show an intra-alveolar collection of amorphous proteinacious material exhibiting a positive stain with periodic acid-Schiff. The aveolar walls are normal in appearance without interstitial thickening being present.

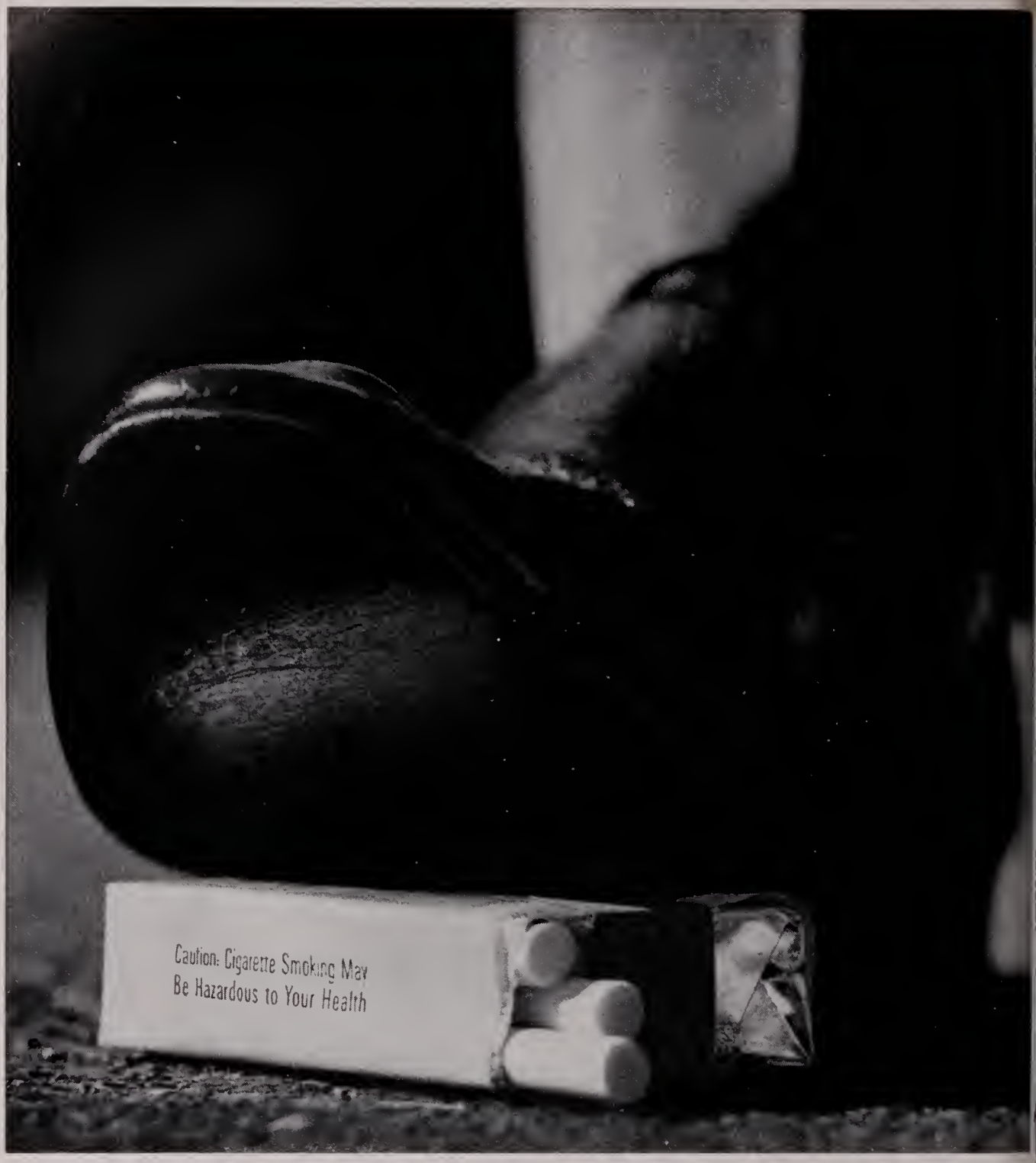
The natural course of the disease is variable and unpredictable. Up to a third of afflicted patients may clear or improve, another third may remain static, and the remainder may progress and terminate fatally. Pulmonary lavage seems to be the most effective treatment, but because of the unpredictable course of the disease this is perhaps best reserved as a modality of therapy for hospitalized patients with progressive disease.

Harold D. Kletschka, M.D.
Montgomery, Alabama

Reference

1. Vidone, R. A., Hoffman, L., Hukill, P. B., Nesbitt, K. A., and McMahon, F. J.: Diagnosis of Pulmonary Alveolar Proteinosis by Sputum Examination. Dis. Chest 49:326, 1966.

Think of the ills from which you are exempt.—Joubert.



If you give up cigarettes, you might gain a few pounds.

(And also a few years.)

The plain, unfiltered fact is that people who smoke cigarettes get lung cancer a lot more frequently than nonsmokers.

And lung cancer can finish you.

Before your time.

We'd rather have you stay alive and in good health.

Because even if you do gain a few pounds, you'll have the time to take them off.

american cancer society

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Dermatology

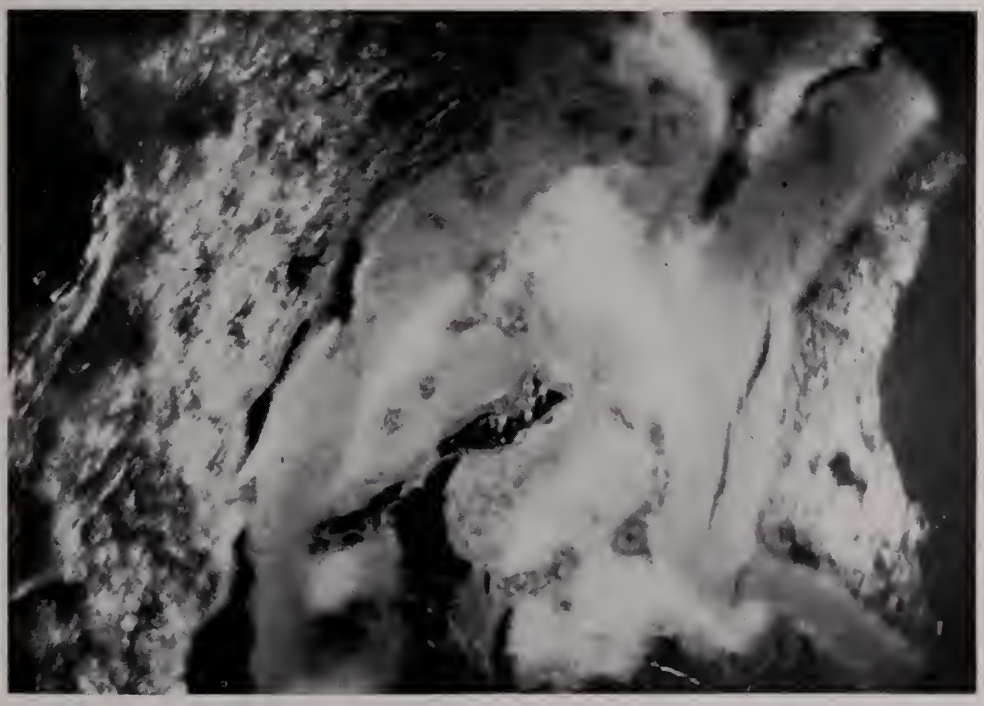
Osteoma Cutis

OSTEOMAS ARE single or multiple ectopic calcareous growths of varying size. They are benign and neither infiltrate nor metastasize. Histologic demonstration of a calcified lamellar structure surrounding lacunae with nuclei and haversian systems* is diagnostic. This structure differentiates an osteoma from calcinosis. Calcinosis cutis refers to amorphous deposits of phosphate and carbonate salts of calcium in the skin. It may occur in certain metabolic and endocrine disorders or be secondary to trauma, neoplasms, and chronic inflammation. Similarily, ossification sometimes occurs in tumors and sites of chronic inflammation. This is secondary, however, and should not be confused with ossification which occurs as a primary event. The term osteoma is preferable for the latter condition.

Secondary ossification and calcification have been reported in calcifying epithelioma of Malherbe, mixed tumor of the skin, basal cell carcinoma, intradermal hairy nevi, fibromas, ulcers, acne vulgaris, dermoid cysts, retention cysts, scleroderma, and lupus erythematosus.

Primary osteoma cutis probably represents a developmental defect. It may be present at birth or develop later in life. The lesions are usually multiple, but they may be solitary. Cutaneous osteomas occur occasionally in association with multiple pigmented nevi.

*See Test Your Word Score, Page 45.



Figure—Photomicrograph of osteoma cutis showing areas of fluorescence due to tetracycline uptake.

Pathogenesis

The pathogenesis of primary osteomas is not known; they may arise from embryonal cysts. Connective tissue, cartilage, bone, and fat may have a common mesenchymal origin with pluripotential capabilities for forming bone. Evidence favors the origin of these osteocytes from mesenchymal cells rather than cartilage. Osteoma cutis thus is a form of membranous rather than enchondral bone.

Analysis of ectopic bone in osteoma cutis has shown that in some respects its character is much like normal bone. Values for calcium and phosphorus fall within the range of values reported for normal bone. Ectopic bone takes up, mobilizes and exchanges calcium just like normal bone. Tetracycline will deposit in both ectopic and normal bone (Figure). All these similarities do not mean that ectopic and normal bone are identical. Differences exist, although the similarities are interesting.

Treatment

Treatment of osteoma cutis is unsatisfactory. It consists of surgical removal of lesions which are growing, painful or subject to irritation.

Willard C. Peterson, Jr., M.D.
Minneapolis, Minnesota

Your Ulcer-Indigestion Index

If you have ever had an ulcer in your stomach or duodenum, you have a proved tendency toward this condition and should take every available step to keep the situation under control. Repeated episodes of nervous indigestion and heartburn also indicate a severe tendency toward emotion-generated digestive upset. But even if you never have suffered these miseries, you may have a mild tendency toward ulcer and indigestion which you can readily combat before it leads to trouble. Add up these scores:

20 points if you're a man. Duodenal ulcers strike eight times as often among males, with stomach ulcers equally common in both sexes.

20 points if you have a long, narrow chest and stringbean build. You're less prone to gall bladder disease with this type of body, but much more prone to ulcer.

20 points if your duties involve taking a lot of guff either from customers, superiors, or companions forced upon you by your position.

20 points if you personally make most of the big decisions regarding your own family's welfare.

20 points if you haven't turned to any other member of your family for advice on an important matter in the last three months.

A total score of 60 or more gives you a more-than-average chance of having digestive troubles. Eighty or 100 makes definite steps to cut this risk worthwhile.*

*John E. Eichenlaub: The Minnesota Doctor's Home Treasury of Unusual Stress Easers, 1964.



Painful night leg cramps...

unwelcome bedfellow for any patient– including those with arthritis, diabetes or PVD

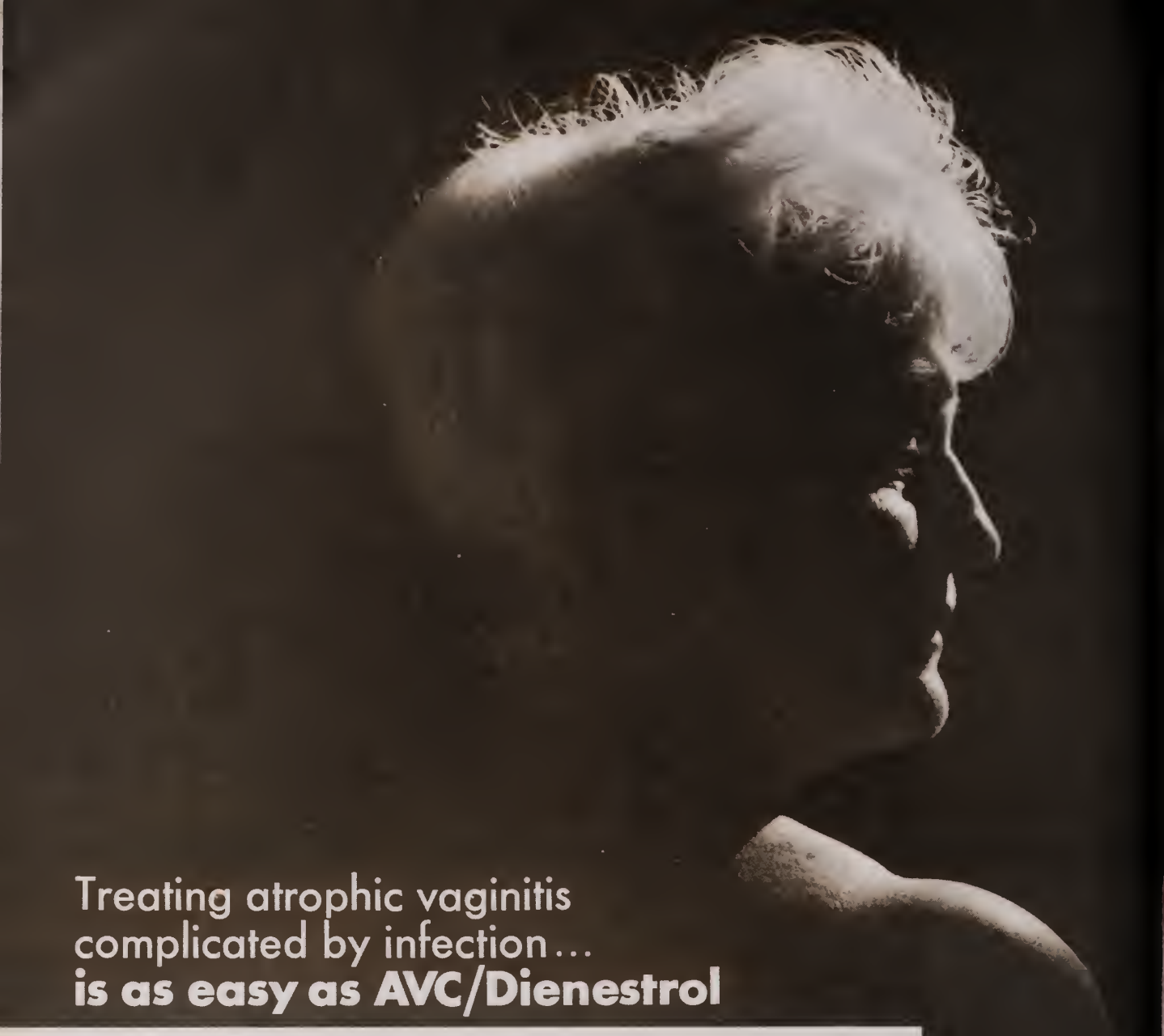
One thing patients can sleep without, particularly patients with chronic disease conditions such as arthritis, diabetes or PVD, is painful night leg cramps. Although seldom the presenting complaint, night leg cramps can tie your patients up in painful knots. Now, just one tablet of QUINAMM at bedtime can usually bring an end to shattered sleep and needless suffering. Your patients will sleep restfully—gratefully—with QUINAMM, specific therapy to prevent painful night leg cramps.

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Contraindications: Known sensitivity to sulfonamides; diagnosis or familial history of carcinoma of the genital tract or breasts; precarcinomatous lesions of the vagina or vulva; palpable uterine fibromyoma; mammary fibroadenoma; depressed liver function.

Precautions/Adverse Reactions: The usual precautions for topical and systemic sulfonamides should be observed because of the possibility of absorption. Burning, increased local discomfort, skin rash, urticaria or other manifestations of sulfonamide toxicity or sensitivity are reasons to discontinue treatment. The use of AVC/Dienestrol does not preclude the necessity for careful diagnostic measures to eliminate the possibility of neoplasia of the vulva or vagina. Manifestations of excessive estrogenic stimulation through dienestrol absorption may occur. These include uterine bleeding, breast tenderness, exacerbation of menstrual irregularity and provocation of serious bleeding in women sterilized because of endometriosis. Endometrial withdrawal bleeding may occur if use is suddenly discontinued.

Dosage: One applicatorful or one suppository intravaginally once or twice daily.

Supplied: "AVC/Dienestrol Cream"—Four ounce tube *with* applicator. "AVC" and "AVC/Dienestrol Suppositories"—Box of 12 *with* applicator.

References: (1) Salerno, L. J.; Ortiz, G., and Turkel, V.: Vaginitis: A Diagnostic and Therapeutic Approach, Scientific Exhibit, presented at the 115th Annual A.M.A. Convention, Chicago, Illinois, June 1966. (2) Nugent, F. B., and Myers, J. E.: Pennsylvania Med. 69:44, 1966.

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Fracture Conference

Complex Monteggia Fractures*

Case 1

Dr. Patrick Kelly:

Previously we discussed one type of Monteggia* fracture—dislocation of the radial head with fracture of the midshaft of the ulna. From this we learned that the ulna should be reduced under direct vision and fixed internally. I think that the method of fixation is the choice of the orthopedist; you can use an intramedullary nail or a plate. It is not necessary to reduce the radial head by an open procedure if you can clearly feel it go back into position and then see it reduced on the roentgenograms.

*Fracture Conference, May 27, 1968.



Fig. 1—(Case 1). Sideswipe injury with resultant compounded Monteggia fracture.

In children these radial heads may not go back into place. This may well be due to the fact that, in a Monteggia fracture in a child, the radial head may slip out of the annular ligaments and then, when you try to push the radial head back in, the intact annular ligament acts like a rubber band holding the radial head out of position. In the adult it is possible for the radial head to go back into position if you stabilize the ulna.

We now want to discuss some more complex Monteggia fractures.

Dr. Donald Paarlberg:

In this case, a 20-year-old man injured his left elbow in an accident in which his automobile left the road and sideswiped a mailbox. He sustained the injury shown in Figure 1.

Dr. Kelly:

Dr. Lilly, what should be done here? This patient has a compound fracture of the very upper part of the ulna, comminution, and dislocation of the radial head.

Dr. Alan D. Lilly:

Was the arm normal neurologically?

Dr. Paarlberg:

There was mild paresthesia to the thumb.

Dr. Lilly:

I would explore the wound and do a debridement. Where was it compounded?

Dr. Paarlberg:

At the proximal fragment of the ulna.

Dr. Lilly:

I think internal fixation of the ulna is needed. I would use a screw or a Knowles pin and try to reduce the radial head at the same time; if it would not reduce, I would do an open reduction of the radial head. If you held that with a lag screw and tightened the screw down you might have some shortening.

Dr. Kelly:

About an inch, I'm afraid.

Dr. Lilly:

I think you could do it with a Knowles pin.

Dr. Kelly:

Or some type of intramedullary fixation. I think you can always assume that the surgeon has had a certain amount of difficulty with any fracture if you see encircling wires on the roentgenogram as you do in this case. This fracture had the consistency of a crushed soda cracker and presented problems.

Dr. Lilly:

Did you have to do open reduction of the radial head?

Dr. Kelly:

No.

Dr. Lilly:

I think I would use a bone graft, although I believe it would heal quite well without one because there is cancellous bone in that location.

Dr. Kelly:

What do you think, Dr. Linscheid?

Dr. Ronald Linscheid:

I would not use a bone graft in this case because I think it would heal quite well without it.

Dr. Kelly:

What do you think, Dr. Johnson?

Dr. Einer Johnson, Jr.:

I would not use a graft either. I am interested in the debridement. Were you able to close it primarily?

Dr. Kelly:

We cleaned it up and closed it primarily. I thought it was probably safe in that area with very little if any muscle involved. But still it was a compound wound.

Dr. Paul R. Lipscomb:

I think I would have left it open and done a closure about six days later and probably not put a graft in at that time.

Dr. Anthony J. Bianco:

I think I probably would have closed it and used a bone graft.

Dr. Kelly:

I tend toward Dr. Lipscomb's point of view. Since there was little involvement of muscle and this was a wound of skin and subcutaneous tissue as well as bone, I thought that after we cleaned up the wound we could close it. The wound was closed very loosely with wire sutures. I did not add bone. I believe that you can assume that this fracture is not going to heal quickly because stability was not secure, and stability is important in the healing of a fracture.

Dr. Paarlberg:

Twelve days postoperatively a long-arm cast was applied. Roentgenograms made two months postoperatively revealed delayed union. Three months postoperatively splints were applied and the patient was encouraged to move



Fig. 2—(Case 1). At five months after open reduction.

the elbow.

Dr. Kelly:

Here is where I made a decision that may not represent the consensus of my colleagues. At that time I was quite certain that there was delayed union (Figure 2) and my reasoning was as follows: There is delayed union; there will be a stiff elbow; I will have to operate on this man again. I wondered if this was the time to follow the tenets of George Perkins, an English orthopedist who believed that motion should be regained in the joints before healing of the fracture. For instance, if you were to visit the wards of St. Thomas' Hospital, you might see a patient with a tibial fracture, with a pin through the os calcis, moving his knee and his tibial fracture simultaneously. Only after adequate knee motion is obtained is the fracture immobilized in plaster cast. My point is to emphasize rehabilitation of joints as well as healing of fractures. What I did was remove the cast and ask the patient not to pronate or supinate the forearm but rather to flex and extend the elbow. After the elbow motion returned, bone grafting of the elbow was undertaken. Dr. Langloh, tell me in detail how you would do this bone graft? Remember, this is a reasonably stable delayed union. Do you favor a double-onlay graft, an inlay graft, a sliding bone graft, or a Phemister type onlay bone graft?

Dr. Nikolaus Langloh:

I think the double onlay.

Dr. Lee C. Detenbeck:

I would do an onlay tibial graft.

Dr. Lilly:

I think I would do a double onlay.

Dr. Kelly:

I am sorry to differ with you, but I thought this should be treated by a Phemister bone grafting procedure. As you know, this involves placing flat, long pieces of iliac bone across an area of fibrous union. You are building a bridge of bone across the non-union, and when this bridge of bone is solid the non-union heals.



Fig. 3—(Case 1). Immediately after placement of onlay bone graft of Phemister type.

Dr. Paarlberg:

It was grafted. Multiple Phemister onlay grafts were placed on the medial and lateral aspects of the ulna (Figure 3). Six weeks later the plaster cast was removed and flexion-extension exercise was started. The roentgenograms at six months after bone grafting are shown in Figure 4.

Dr. Kelly:

In this view you see a good solid bridge of bone across the site of nonunion. The patient is free of pain.

Dr. Paarlberg:

At that time he had elbow motion from 120° to 40°. Pronation and supination were limited by 10°.

Dr. Kelly:

It finally united. We took the pin out and the patient is back at heavy labor now. Dr. Johnson, would you like to comment on that?

Dr. Johnson:

I approve of your method of grafting, but I think I would not graft it when you did. You did not say you removed the wires, but you did remove them because you could not have put the grafts on without doing so. You used the Steinmann pin in this case, and I think this is all right. I have used Steinmann pins with success at times. The best thing about them is that they come in a greater variety of sizes and you do not have to spend a lot of time making them fit and so lose what medullary bone formation you have. They are easy to insert. They do stick out of the skin, but that does not mean that they do not work. I would originally have left the wound open, used the fixation you did, and closed the wound five to seven days later. It looked as if it



Fig. 4—(Case 1). At six months after bone graft procedure, showing bony union across fracture site.

could be closed with safety. What is the range of motion now?

Dr. Kelly:

He lacked 10° of full pronation and supination and, at the last time we saw him, he lacked about 10° full extension. I would certainly agree that you could use intermedullary fixation in these upper ulnar fractures. I agree with you, too, that the Steinmann pin does provide probably the largest selection of diameters and lengths for simplicity of fixation for this fracture. These comminuted fractures of the upper end of the ulna are a totally different problem from the Monteggia with a fracture toward the midshaft of the ulna. As Dr. Johnson pointed out, it is difficult to immobilize the comminuted fractures. Let us proceed to the next case.

Case 2

Dr. Paarlberg:

A 73-year-old woman was in an automobile accident in which she sustained a ruptured right globe, a fractured zygoma, multiple facial lacerations, a fractured left humerus, and injuries to the right elbow (Figure 5).

Dr. Kelly:

This compound fracture of the elbow was eight hours old when we were called to treat the patient just after she had undergone extensive surgical treatment for her facial injuries.

Dr. Richard H. Turner:

First the wound should be debrided. At this stage I wonder if it might make the problem easier if the radial head were excised.

Dr. Edwin L. Laurnen:

I think shortening the radius would slow healing, and the chances of infection would be greater if radial head excision were performed.

Dr. Sherwin Goldman:

Debride the wound and, depending on the skin loss, decide whether to close or leave the debrided wound open. I probably would reduce the fracture.

Dr. Kelly:

In what position are you going to put the forearm so that reduction will be maintained? Are you going to flex the elbow beyond 90°, leave the elbow at 90°, or extend the elbow?



Fig. 5—(Case 2). Compound Monteggia fracture in 73-year-old woman.

Dr. Goldman:

The elbow should be immobilized at 90°.

Dr. Kelly:

Dr. Mess, what would you do?

Dr. Charles F. Mess:

Flex it beyond 90°.

Dr. Kelly:

The circulation was very good, with bounding radial and ulnar pulses. Dr. Mess is correct, as shall be subsequently shown. In this type of Monteggia fracture, flexion of the elbow will maintain reduction of the radial head.

Dr. Kelly:

Right! This patient's critical condition suggested to all of us at the scene that debridement and packing of the wound and immobilization of the fracture were the simplest method of treatment (Figure 6). After two weeks it was decided that the radial head would stay in position. Then it was our decision to extend the elbow to obtain better position of the ulnar fracture. Flexing the elbow in this fracture with a short ulnar proximal fragment tends to lead to angulation of the ulnar fracture.



Fig. 6—(Case 2). Immediately after debridement and reduction.

Dr. Paarlberg:

Two months postoperatively the plaster cast was removed and the patient was allowed to start mobilizing the elbow. At this time a clinical union seemed to have occurred, although roentgenographic evidence of complete union was lacking. The patient was dismissed three months after the injury, with 140° to 55° of motion in the right elbow. She was seen again one year and three months later (Figure 7).



Fig. 7—(Case 2). At one and a half years after injury fracture shows solid union.

Dr. Kelly:

See how nicely those fragments have lined up. The point to emphasize in this case is that, although Monteggia fractures usually require open reduction, there are exceptional cases in which the rule does not hold. We began this conference by saying that you open all Monteggia fractures, but to every rule there is an exception. If you have a patient who is this seriously injured, I think you should do the simplest thing that might give a tolerable result. This patient is doing well now and is taking care of herself completely. She is a very strong and vigorous woman. Except for a slight lack of extension, she has an almost normal elbow.

Dr. Bianco:

You must consider that excision of the radial head would have sacrificed the only chance of maintaining the length of the arm.

Dr. Kelly:

If there is one thing you should not do in a Monteggia fracture, it is excise the radial head.

Dr. Lipscomb:

I certainly would agree. I think you have to remember that, with radial head dislocation, the interosseous membrane is torn sharply.

Dr. Johnson:

Of the many interesting things you have said, I believe one should be repeated. Often in the average book on fractures there will be a statement that, when the ulna is reduced (this is fairly easy to do) by closed means, the radial head always lines up again.

Dr. Kelly:

I think this is true in some fractures in children but not in all. Usually in the adult the radial head will go back.

Dr. Johnson:

Yes, but the point I am making is that you can easily line up the ulna. The idea the books always imply is that the ulna is easy to reduce, usually by closed means, but it has never been so in my practice.

Dr. Kelly:

It's a problem of maintaining stability of the ulna. Usually you have to resort to internal fixation to maintain stability. Dr. Stauffer?

Dr. R. N. Stauffer:

I would just like to say something about the plate versus the intermedullary rod. I wonder if you do not have a great deal more resistance to torsional stress with a plate than with the Steinmann pins.

Dr. Kelly:

I would agree to using a plate if the fracture is more distal than it was in these two patients, if the fracture is not compound, and if the fracture is not severely comminuted.

Let me summarize our conference: Most Monteggia fractures in children are easily reduced by closed methods and held in plaster casts until healed. In exceptional instances the radial head may not reduce and the orbicular ligament may actually block reduction. In young adults with a dislocated radial head and a clean-break type of ulnar shaft fracture, reduction and fixation of the fracture with a plate or intramedullary rod will be sufficient. In this instance the radial head will often reduce and remain reduced without operation on the radial head region. Lastly, we have the "sideswipe injuries," which are very unstable fractures with a great deal of comminution and are often compound. In this situation healing of the wound is essential. Often

there are associated injuries that take priority. We have presented two cases to illustrate the difficulty in treating these fractures.

Patrick J. Kelly, M.D.*
Donald Paarlberg, M.D.*
Einer W. Johnson, Jr. M.D.*

Rochester, Minnesota

*From the Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

Nobel Prize Winners

In Medicine and Physiology
1934

George H. Whipple, George R. Minot, William P. Murphy

For their discoveries concerning liver therapy against anemias.

"The idea that something in food might be of advantage to patients with pernicious anemia was in my mind in 1912, when I was a house officer at the Massachusetts General Hospital.

"The study of the patients' diets was begun in 1915 in an attempt to determine if some sort of dietary deficiency could be found.

"For centuries the concept that food bore a relationship to anemia had been vaguely expressed in the literature. It had been shown that liver and kidneys, rich in complete proteins, promoted the growth of animals, and that substances in liver could enhance cell-division. It was likewise recognized that liver-feeding could benefit patients with sprue and pellagra.

"A few patients were fed relatively small amounts of liver during 1924 and early 1925. Although these patients did better than expected, the results permitted no more than speculations. Then Dr. Murphy joined in the work and we pursued the study of these and subsequent cases. Liver had been fed by Gibson and Howard and other individuals to pernicious anemia patients but without persistence or definite results. It seemed to us that to accomplish our object a large weighed amount of liver should be fed daily with regularity. . . . By May, 1926, we had fed liver intensively and daily to 45 patients. In many of these patients symptomatic improvement was obvious within about a week. Soon they craved food and color appeared in their faces. Tongue and digestive symptoms rapidly lessened. Within about 60 days the red blood cell counts had risen on the average from low levels to approximately normal. . . . An objective measure of the effects upon blood-production was the chief basis of our conclusions that by feeding liver significant improvement had been obtained."*

The practical results of liver therapy in the treatment of pernicious anemia have been indicated in quotations from the Nobel lectures of Dr. Minot. Another agent subsequently introduced for the same purpose was a preparation of the stomach wall of the hog—desiccated, defatted and powdered. Its effect is similar to that of liver. These organ extracts have now been joined by vitamin B_{12} in the treatment of the disease.†

*G. R. Minot: The Development of Liver Therapy in Pernicious Anemia, 1934.
†Theodore Sourkes: Nobel Prize Winners in Medicine and Physiology, 1966.

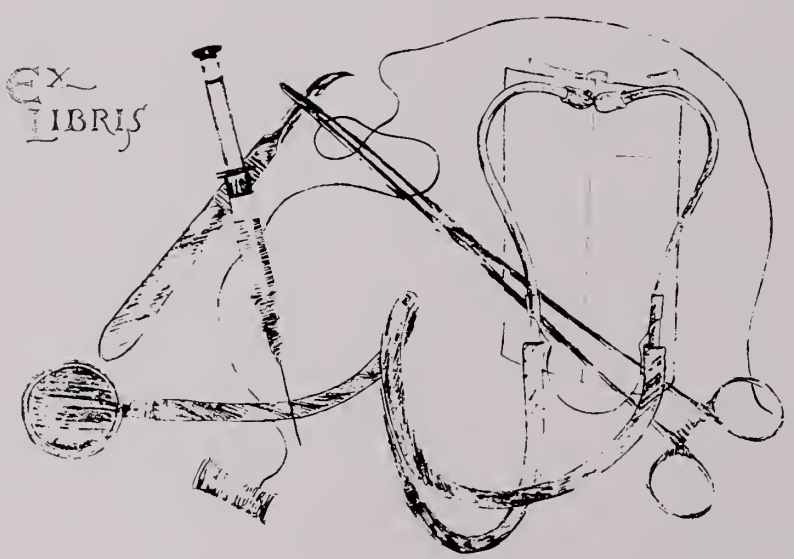
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Carl O. Rice, M.D.



Case Reports

Pre-eruptive Varicella Encephalitis Presenting as Status Epilepticus

CLINICALLY EVIDENT encephalitis as a complication of varicella occurs in less than 1/1000 (0.1%) cases,[1] although in patients hospitalized with varicella the incidence is 0.26%[2] to 0.3%.[3] Electroencephalographic abnormalities have been reported in 22% of supposedly uncomplicated varicella.[4] The majority of cases are post-eruptive. However, there have been sixteen cases of pre-eruptive varicella encephalitis reported to date.[5-9] The present case emphasizes the need to make careful inquiry regarding the exposure to known infections in a child who presents with status epilepticus of unknown etiology.

Case Report

Present Illness

A six-year-old Caucasian female, was admitted to Hennepin County General Hospital on April 26, 1968, in status epilepticus. She had been well until April 24, when she complained of pain behind her left ear. The following day she complained of pain in her occipital area. There was no known history of exposure to toxins or drugs; however, the patient had been exposed to varicella at school three to four weeks prior to admission.

Early Appearance of Convulsive Activity

On the morning of admission she had a mild cough and rhinitis but no fever. After playing outdoors she complained of dizziness and was unable to focus her eyes or "use her hands." Over the next few minutes she became unresponsive, began vomiting, and developed focal motor seizures with tonic-clonic movements starting in the right arm and eyes deviating superiorly and to the right. The seizure became generalized with right-sided predominance and continued over the next hour.

Neurological Status

On admission her blood pressure was 96/60, her pulse 120/minute, her respirations 28/minute, and her temperature 98° (axillary). She was unresponsive, had shallow, noisy respirations and constant tonic-clonic movements of her right arm and leg, with her eyes deviated to the right and superiorly. The cranial nerves were intact and the pupils were midposition and reacted to light. Funduscopic examination was normal. The tendon reflexes were hyperactive, with bilateral, unsustained, coarse ankle clonus, and bilateral Babinski signs. Her muscle tone was decreased and there was normal response of all extremities to deep pain only. The remainder of the physical examination revealed a left otitis media characterized by a diffusely red, injected, and bulging tympanic membrane.

Laboratary Data

Initially the seizures were controlled with intravenous Valium (2.0 mg.) and rectal paraldehyde. A lumbar puncture revealed clear fluid with an opening pressure of 225 mm. The cerebrospinal fluid had 14 WBC (all mononuclear), 10 RBC; the protein was 42 mg. %. and the glucose 78 mg. %. Smear and culture of the fluid were negative. The following laboratory data were obtained: hemoglobin 13.5 gm. %, leukocyte count 12,800 (neutrophils 71%, lymphocytes 24%, and monocytes 4%), Na^+ 141 meq/L, K^+ 3.8 meq/L, Cl^- 104 meq/L, Co_2 content 24 meq/L, Ca^+ 10.0 mg. %, and glucose 130 mg. %. Roentgenograms of the skull and chest and a brain scan were normal.

Hospital Course

The patient was subsequently treated with intravenous ampicillin, until culture of the cerebrospinal fluid was reported to be negative, and with phenobarbital and dilantin as anticonvulsant medication. She became alert and responsive six hours after admission, and the plantar responses became flexor. By the fourth hospital day the cerebrospinal fluid was normal. An electroencephalogram performed on that day was "moderately abnormal" because of scattered spikes in the right central, right posterior temporal, and left occipital regions, with high amplitude sharp wave activity also in the left occipital region.

Appearance of Rash

On the fifth hospital day she became lethargic with postprandial vomiting, and then developed a frontal headache with slight nuchal rigidity, which disappeared later except for the vomiting and mild lethargy. On the sixth hospital day she developed a typical varicella eruption on the trunk and face. The remainder of the hospital course was uneventful, and she was discharged on the seventh hospital day with no neurologic abnormalities. Acute and convalescent serum showed a rise in complement fixation titers of less than 8 to more than 128 against varicella (performed by the Minnesota State Board of Health). Virus isolation from specimens of stool, pharyn-

geal washings and cerebrospinal fluid was unsuccessful.

The patient was placed on phenobarbital, 30 mg. t.i.d., for seizure prophylaxis and, when seen as an outpatient one month later, was normal neurologically and had had no further seizures. An electroencephalogram performed at this time, however, was "moderate to markedly abnormal" because of diffuse lateralized slow activity and spike activity in the left hemisphere. This was interpreted as being more abnormal than the previous tracing. She was seen two months after discharge, was clinically normal, and the electroencephalogram showed "marked improvement," with only increased slow activity over the left hemisphere.

Discussion

Encephalitis comprises about 90% of the neurologic complications of varicella, with the remaining 10% being mainly myelitis and polyradiculitis. There is a definite preponderance of males in all series, the ratio being 2:1.[2,5,10] The average latent period from the time of the eruption to the onset of neurologic symptoms is 6.3 days, with most cases being involved between the third and eighth days.[2] Signs and symptoms of cerebral involvement, namely, meningoencephalitis, changes in sensorium, and occasionally coma and convulsions occur in the majority of patients. Involvement of the cerebellum, resulting in ataxia, vomiting, speech changes, nystagmus, vertigo, and tremor, is very common, being reported in 34% of cases.[2,10]

In 1935 Underwood[5] reviewed the neurological complications of varicella and reported eleven cases of pre-eruptive varicella encephalitis. The latent period before the eruption varied from one half to eighteen days, with the mean being 38 days. The predominant feature of these cases was convulsions, which lasted from two to thirty minutes, and were usually associated with an elevated temperature. All of these cases were reported as "cured."

Faust[6] reported a case that presented eight days pre-eruptive with backache, headache, and convulsion, with a temperature of 105° during the course of his illness. His patient was reported to be normal on follow-up examination two months later. Holliday[7] added another case that began with seizures occurring three to four times daily with the onset being coincidental with the time of eruption. His patient continued to have seizures, with gradual deterioration and died one year later. Wallace[8] reported a patient with a right facial and hypoglossal nerve palsy which developed seven days before the eruption. Six months later there was a mild facial nerve weakness remaining. Most recently reported is a case of Goldston and associates:[9] a patient with cerebellar ataxia with signs and symptoms of increased intracranial pressure eleven days before the eruption of typical varicella skin lesions. The patient was afebrile, had evidence of congenital communicating hydrocephalus, and made a complete recovery.

The patients who die from varicella encephalitis usually do so in the first week of the illness, while the average duration of symptoms in those without complications is two to three weeks. Ataxia would seem to be a favorable early sign, for very few cases with this symptom are fatal.[5,11] Coma, convulsions, or both are ominous signs, with a higher mortality rate and more serious sequelae.[2,10] The mortality of patients in whom coma occurred was over 40%; in those with convulsions, over 30%; and in those with both, over 60%.[11] The overall mortality has been reported as 5%[2] to 10%.[11] Sequelae have been reported in between 15% and 20% of cases and include behavior disorders, retarded mental development, seizure disorders, and occasionally blindness, paralysis, or speech disorders.[2,10,11]

Treatment of varicella encephalitis is nonspecific, as for most viral encephalitides, and is primarily supportive, with correction of the complications that may develop. Appelbaum[2] suggested that the use of corticosteroids might be helpful in the early phase of varicella encephalitis. A study of two patients with varicella encephalitis, however, revealed normal cortisol production rates and showed no evidence to support the use of corticosteroids.[12]

The etiology of varicella encephalitis is unknown; there are no reports to support any of the proposed theories: (1) invasion by a neurotropic virus, (2) activation of a latent virus, or (3) an allergic reaction. The present example of pre-eruptive encephalitis would be more compatible with direct neurotropic action of the varicella virus during the period of generalized viremia; however, this is only speculative. Although no conclusions can be drawn from this case as to the pathogenesis of the para-infectious encephalitides, it is hoped that more case reports may furnish some evidence.

Conclusion

A case is reported of pre-eruptive varicella encephalitis, presenting as status epilepticus preceding the typical varicella eruption by six days. The patient had an uneventful clinical recovery. However, when she was last seen, there was residual electroencephalographic abnormality.

I wish to thank Dr. Francis S. Wright for his helpful suggestions in reviewing this manuscript.

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Purely Personal

Henry L. Mencken once wrote an essay in which he observed that as one grows older, more and more of the people with whom one has been in close association through the years pass on so that one becomes accustomed to the concept of an approaching end. Indeed there have been some whose lives have been so full of toil and sadness and tribulation and who have been so terribly harassed and prodded and criticized that they have welcomed the approaching end. People live so much longer now than they did formerly—and here I am now near to eighty and really having a wonderful time. Just before I was seventy-eight I was still hopping about from place to place making speeches for all sorts of hospitals, medical schools, forums, clinics, and organizations. In less than forty-eight hours I had traveled coast to coast, with side trips from San Francisco and from New York. It proved a little too much for me. My doctors, in their quaint vernacular, "gave me the works," which included all the laboratory tests of blood, any other fluids that could be taken from the body with a variety of instruments, an electrocardiograph, an electroencephalograph, the use of radioactive isotopes, motion pictures of the bowel from top to bottom (quiet and in action), psychological tests, psychiatric tests—in a few words, "the works." They told me to take off twenty pounds, and I stayed in the hospital until I got the twenty pounds away. A year and a half later, ten had come back, and now I am working at getting those ten off again. I am inspired to this action by a little walk I took with my granddaughter on Easter Day. She said to me wisely, "Grandpa, you don't have to worry about getting fat. You are already there."

Well, that's life!*

*Morris Fishbein: An Autobiography, 1969.

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(Continued to page 114)

Laboratory Letter

The Use of Sodium and Potassium in the Office

ARE THERE conditions for which you might order serum sodium and serum potassium in the office?

Yes, more than you might think: congestive heart failure, chronic renal insufficiency, endocrine disorders (Cushing's syndrome, Addison's disease, pituitary lesions, or primary aldosteronism), and chronic diarrhea, malabsorption, or vomiting. And what of patients on long-term steroids or diuretics? Any of these disorders or drugs can cause electrolyte problems.

Why then, are not these tests ordered more often? Probably, I suspect because of expense and inconvenience. Before modern flame photometers were developed to their present state of simplicity and precision, sodiums and potassiums were cumbersome procedures and not very reliable at that. Now these two tests are the most accurate, precise, and reproducible of serum chemical tests. And because of the ease of measuring these substances, the cost of doing them has dropped. Until recently, flame photometers were present only in hospitals, making the ordering and transport of office samples difficult. With photometers in reference laboratories, this is no longer the case.

Let's consider two conditions in which a serum sodium and potassium may prove useful.

Heart Failure

Probably the most common and difficult of electrolyte problems in patients with heart failure is dilutional hyponatremia. This usually occurs when the heart falters so badly it can no longer adequately perfuse the kidneys. As ischemia progresses, the kidneys become incapable of producing a dilute urine, and a low serum sodium results.

In some patients with congestive failure, a low serum potassium is also a problem. The mechanism seems to be this: To conserve sodium, the kidney exchanges potassium for sodium. Hypokalemia follows. Moreover, thiazide diuretics can exaggerate potassium loss. Indeed, these diuretics can produce hypokalemia six to eight days after therapy starts.

If the physician prescribes supplemental potassium, the converse condition—hyperkalemia—may occur. This usually happens when the kidney is avidly retaining sodium. Little sodium then reaches distal tubules, where sodium for potassium exchange takes place. With no sodium to exchange, potassium cannot be excreted. In short, diuretics can give rise to hypokalemia, and diuretics plus potassium can cause hyperkalemia. For these reasons, Doctors Walker and Cooke of Johns Hopkins have recommended that in persons in failure, "it is important to check the serum potassium at regular intervals, even in patients who appear stable."[1]

Hypertension

According to Jerome Conn, Professor of Medicine at the University of Michigan who first described primary aldosteronism in 1954, most patients with aldosterone-secreting adenomas have hypertension, increased body sodium, and renal potassium wasting.[2] Many will have a low serum potassium, though some patients with "essential" hypertension can be normokalemic and still have an adenoma.[3] In any case, serum potassium is a simple screening test for picking up hypokalemic aldosteronism. If it is low in a patient with

hypertension (provided he has not been on diuretics), you may have made an important first step in diagnosing a surgically correctable lesion. A serum potassium is the best single screening test for primary aldosteronism.[4] If the patient is taking diuretics, they ought to be discontinued for one week, and sodium and potassium measured in a 24-hour urine collection. Decreased plasma renin also indicates primarly aldosteronism, but only a few laboratories measure this substance.

Richard L. Reece, M.D.
Minneapolis, Minnesota

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Moderation or Excess

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Us'd or abus'd do men much good or harme.

—Regimen Sanitatis Salerni

Editor's note: This couplet affirms the polarization of use and abuse. Who could say it better?

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  Some bring it in a pot,
Some bring a sample hardly ample,
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Some, quite undaunted, proudly flaunt it
  As if it gives them pleasure.

Some cork it up so tightly that
  It's quite a job to spring it,
Some let it slosh, almost awash,
  And some forget to bring it.

Richard Armour: The Medical Muse, 1963.

Circumstances

The people who get on in this world are the people who get up and look for the circumstances they want, and, if they can't find them, make them.—George Bernard Shaw

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Warning: If coumarin-type anticoagulants are given simultaneously, watch for excessive increase in prothrombin time. Instances of severe bleeding have occurred. Persistent or severe dyspepsia may indicate peptic ulcer; perform upper gastrointestinal x-ray diagnostic tests if drug is continued. Pyrazole compounds may potentiate the pharmacologic action of sulfonylurea, sulfonamide-type agents and insulin. Carefully observe patients receiving such therapy. Use with caution in the first trimester of pregnancy and in patients with thyroid disease.

Precautions: Before prescribing, carefully select patients, avoiding those responsive to routine measures as well as contraindicated patients. Obtain a detailed history and a complete physical and laboratory examination, including a blood count. Patients should not exceed recommended dosage, should be closely supervised and should be warned to discontinue the drug and report immediately if fever, sore throat, or mouth lesions (symptoms of blood dyscrasia); sudden weight gain (water retention); skin reactions, black or tarry stools or other evidence of intestinal hemorrhage occur. Make complete blood counts at weekly intervals during early therapy and at 2-week intervals thereafter. Discontinue the drug immediately and institute countermeasures if the white count changes significantly, granulocytes decrease, or immature forms appear. Use greater care in the elderly and in hypertensives.

Adverse Reactions: The more common are nausea and edema. Swelling of the ankles or face may be minimized by withholding dietary salt, reduction in dosage or use of diuretics. In elderly patients and in those with hypertension the drug should be discontinued with the appearance of edema. The drug has been associated with peptic ulcer and may reactivate a latent peptic ulcer. The patient should be instructed to take doses immediately before or after meals or with milk to minimize gastric upset. Drug rash occasionally occurs. If it does, promptly discontinue the drug. Agranulocytosis, exfoliative derm

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s, Stevens-Johnson syndrome, ell's syndrome (toxic necrotizing dermolysis),or a generalized rgic reaction similar to serum kness may occur and require rmanent withdrawal of medication. Agranulocytosis can occur ddenly in spite of regular, repeated rmal white counts. Stomatitis d, rarely, salivary gland enlargent may require cessation of treatnt. Such patients should not ceive subsequent courses of the ug. Vomiting, vertigo and languor y occur. Leukemia and leukemoid ctions have been reported. While t definitely attributable to the ug, a causal relationship cannot be excluded. Thrombocytopenic purpura and aplastic anemia may occur. Confusional states, agitation, headache, blurred vision, optic neuritis and transient hearing loss have been reported, as have hyperglycemia, hepatitis, jaundice, hypersensitivity angiitis, pericarditis and several cases of anuria, glomerulonephritis and hematuria. With long-term use, reversible thyroid hyperplasia may occur infrequently. Moderate lowering of the red cell count due to hemodilution may occur.

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Advances

Chronic Mucocutaneous Candidiasis

Its Association with Immunologic and Endocrine Abnormalities

Thrush or subacute *Candida* infection of the oral cavity is a relatively common condition. Thrush may occur as a complication of an underlying chronic and serious illness, such as carcinoma or lymphoma, or when iatrogenic factors have altered the immunologic defense mechanisms or the flora of the host.[1] Among the iatrogenic factors favoring the development of candidiasis are antibiotic therapy, corticosteroids, and antimetabolites.[1] Dissemination of the infection may also occur in such patients.[2]

To be clearly separated from thrush is a chronic infection due to *Candida* species (usually *C. albicans*), which involves the oral cavity simultaneously with the fingernails and certain areas of the skin and has been designated as "chronic mucocutaneous candidiasis."[1] One remarkable feature of this type of infection is that it is extremely resistant to all forms of topical therapy.[1,3] Amphotericin B has been resorted to for the treatment of some cases and has resulted in temporary eradication of the chronic superficial *Candida* infection.[3] This antifungal agent has the disadvantage of being effective only when given intravenously and, because of its potential nephrotoxicity, should not be used without great care.

Chronic mucocutaneous candidiasis is known to be associated with certain uncommon endocrine disorders[1] and immunologic deficiency syndromes. It may also occur as an idiopathic entity. The diagnostic considerations that should be entertained when chronic superficial candidiasis is encountered are listed in the Table.

Familial Juvenile Hypoparathyroidism, Hypoadrenocorticism, and Chronic Mucocutaneous Candidiasis

The first reference in the literature to an association of a chronic superficial *Candida* infection with hypoparathyroidism is probably the report by Thorpe and Handley[4] in 1929, but the familial combination of candidiasis and hypoparathyroidism was not described until 1943.[5] It is evident from reported cases that the association of the two abnormalities occurs in such a manner that one of the two conditions, usually the candidiasis, had its onset in childhood.

An important observation is that superficial candidiasis may exist in association with primary hypoparathyroidism but that candidiasis does not complicate the hypocalcemia seen in chronic tetany owing to inadvertent parathyroidectomy in the course of thyroidectomy.[5,6] Chronic superficial candidiasis may also occur in combination with primary adrenocortical insufficiency,[7-9] but it is not a complication in tuberculous Addison's disease.

The Triad

There is a remarkable association of the three diseases—candidiasis, primary hypoparathyroidism, and primary Addison's disease—in some individuals and in certain families as well.[10,11] The triad was given its designation "syndrome of familial juvenile hypoadrenocorticism, hypoparathyroidism and superficial moniliasis" by Whitaker and co-workers.[10] To these three elements of the triad, McIntyre and Gass[12] added a fourth component, chronic keratoconjunctivitis, because of its frequent occurrence. It should be emphasized that the association of the four elements in one individual or in a family is seen almost exclusively in children.[13]

The most common sequence of events[13] is the onset of superficial candidiasis in childhood, anywhere from the age of six months to 14 years (average age, four years). This is then followed by the manifestations of

hypoparathyroidism (tetany with hypocalcemia and hyperphosphatemia) from soon after the onset of candidiasis to up to 13 years later (average interval, 3½ years). Addison's disease, clinically expressed by weakness, shock, and often death, may coincide with or follow the manifestations of hypoparathyroidism. In only a few instances does Addison's disease precede hypoparathyroidism or occur as the only endocrine manifestation after the candidiasis.

Other Disorders

As if this array of pathologic conditions were not perplexing enough, in some patients with the syndrome one of the following disorders may be present: malabsorption,[14-16] chronic liver disease,[17] achlorhydria,[9] pernicious anemia,[9,18] malfunction of the thyroid gland (such as Hashimoto's disease[9]), pulmonary infiltrates of undetermined cause,[4,8] and Schilder's disease.[9] Each one of these disorders occurs more often in this disease complex than can be expected by chance association alone.

DiGeorge and Paschkis[15] stressed that not all of the cardinal elements of the syndrome need be present in the same individual or in a single family. Sporadic cases of hypoparathyroidism and Addison's disease with or without superficial candidiasis, sporadic cases of idiopathic hypoparathyroidism associated with chronic candidiasis, familial cases of hypoparathyroidism, familial cases of Addison's disease, familial cases in which the triad was present in several siblings, and instances of Addison's disease in one sibling and idiopathic hypoparathyroidism in another sibling have been reported.[15]

Primary hypoparathyroidism and primary Addison's disease may also have their onset in adult life.[6,9,19] Clinically, adult cases differ from the childhood syndrome by virtue of rarity of the coexistence of the two endocrinopathies in one individual and the virtual absence of candidiasis in the adult cases. The frequency of other associated diseases is also much lower in adults but, when they do occur, thyroid abnormalities are the most common in contrast to childhood cases.

At autopsy,[12,20] severe atrophy of the adrenal cortex may be noted and frequently the parathyroid glands either cannot be found or are detected only microscopically as small remnants after an exhaustive search. In the early stages of the disease, large abnormal residual cells with hyperchromatic nuclei may be found in the collapsed adrenal cortex. The most common finding is a variable degree of lymphocytic infiltration in the adrenal cortex, the parathyroid remnants, or both. There may be a similar infiltration of lymphocytes in other organs such as the thyroid gland or liver.

Organ-Specific Antibodies

The type of diseases associated with the central features of the triad and the lymphocytic infiltration in various organs logically led to a search for so-called auto-antibodies.[9,19,21] Indeed, the incidence of organ-specific antibodies has been high in the patients with primary hypoparathyroidism and primary Addison's disease. Organ-specific antibodies have been detected which react with parathyroid cells, adrenocortical cells, parietal cells of the stomach, intrinsic factor, and thyroid cells. In relatives of a patient who had primary Addison's disease, keratitis, steatorrhea, hypothyroidism, and candidiasis, antibodies were also found which reacted with uvea and colon cells.[21] A high incidence of rheumatoid factor was noted in this same family. Persons with the various auto-antibodies mentioned did not necessarily have overt or occult disease of the functional cells against which the antibodies were directed.

Pathogenic Mechanism

The cause of the syndrome of chronic superficial candidiasis, hypoparathyroidism, and primary Addison's disease is not known and the pathogenic mechanisms involved are not understood. It is quite evident from the studies on antibodies which react with parathyroid cells, adrenocortical cells, and other tissues and which may predominate in certain families that there exists, in individuals bearing the syndrome, a peculiar propensity of the immunologic apparatus to elaborate species of antibody capable of self-recognition.[9,19,21] However, the presence of such antibodies does not necessarily imply that they are part of the mechanisms which initiate the disease. Such

antibodies may merely be indicators of alteration of antigens naturally present in the target organs, so that the immunologic apparatus will react to these as to "foreign" antigens.

Some students of the disease have suggested that viral agents may be etiologically involved,[5,7] perhaps in the triggering event. In several instances the disease became manifest shortly or some time after measles[4,5,16] (personal observations [P.E.H.]), or it was associated with liver disease indistinguishable from hepatitis.[17] If viruses play any role in the initiation or acceleration of the process which encroaches on the various organs involved in the syndrome, one must still assume an altered or abnormal host response, because the implicated viruses are so prevalent and the syndrome is so rare.

The superficial *Candida* infection is not a likely contributor to the development of the endocrinopathies and other abnormalities of the syndrome. This view is supported by the clinical observation that occasionally the endocrinopathy has preceded the candidiasis and that primary Addison's disease coexisted with primary hypoparathyroidism in patients who did not have associated candidiasis but whose siblings were infected by the fungus. The concept which is in best harmony with the known facts is that the candidiasis is a superficial expression of undetermined abnormalities already present in the host and which favor the development of the infection as well as the endocrinopathies.

Conditions with Congenital Abnormalities of Thymus

Dysplasia of Thymus with Agammaglobulinemia (Swiss-Type Agammaglobulinemia)

Children born with this hereditary disorder invariably die of their disease within the first three years of life, regardless of the treatment used. The disease was first recognized in two children by Glanzmann and Riniker[22] and was named "essential lymphocytophthisis," a designation which reflects the severe lymphocytopenia and the depletion of lymphocytes of peripheral lymphoid organs such as spleen and lymph nodes. The thymus is small and may be ectopic; it is arrested in its epithelial stage of embryologic development.

Two other groups of Swiss investigators[23,24] emphasized the second hallmark of the disease, the agammaglobulinemia. In recognition of the contributions of the three groups of Swiss investigators, the disease is commonly referred to as "Swiss-type agammaglobulinemia." The prevalent type of infection in children who have thymic dysplasia with agammaglobulinemia is a superficial mucocutaneous candidiasis.[22-25] In some of these children the infection has been very extensive and has involved the pharynx, the esophagus, the lower gastrointestinal tract, and the bronchial tree in addition to the oral cavity.[25] In a few instances, disseminated candidiasis has been observed, and at least one case of *Candida* meningitis has been reported.[25]

In common with children who have the relatively more frequent Bruton-type agammaglobulinemia (sex-linked recessive type),[26] children with Swiss-type agammaglobulinemia have an inability to produce functional antibody. Yet it is well appreciated that children with Bruton-type agammaglobulinemia do not have an increased incidence of candidiasis but do have recurrent respiratory tract infections caused by *Haemophilus influenzae* and by pyogenic microorganisms such as *Diplococcus pneumoniae, Staphylococcus aureus,* and various streptococci. The thymus is morphologically normal in Bruton-type agammaglobulinemia and the mechanism of delayed-type hypersensitivity (a function of the thymus-dependent small lymphocytes) is intact.[27]

Bruton-type agammaglobulinemia is an example of dissociation of the two main modalities of the immunologic apparatus—normal thymus and dependent delayed-type hypersensitivity reactions versus abnormal plasma cell-antibody system.[27] A similar dissociation can be observed in acquired idiopathic hypogammaglobulinemias. Members of our group have also noted this dissociation in the syndrome of nodular lymphoid hyperplasia of the small intestine.[28] One patient with this syndrome responded to a tuberculous infection with conversion of delayed-type skin reactivity while he was unable to resist pyogenic infections normally.[29] In contrast, children with Swiss-type agammaglobulinemia have only a rudi-

mentary thymus and severe lymphocytopenia, and they fail to develop delayed-type hypersensitivity reactions.[27] That lymphocytes play an important part in the development of the granulomatous lesions so characteristic of tuberculous and certain deep-seated mycotic infections is well appreciated. It seems appropriate to attribute to the dysfunction of the thymus-lymphocytes-delayed-type hypersensitivity modality in the Swiss-type agammaglobulinemia some essential role among the factors which lead to the development of candidiasis.

Thymic Dysplasia Without Agammaglobulinemia (Nézelof-Allibone Syndrome)

Nézelof and associates[30] in France and Allibone and co-workers[31] in England each described one patient who had all the features of Swiss-type agammaglobulinemia with the exception of the agammaglobulinemia. The thymus was arrested in the epithelial stage of development and lymphocytopenia was severe. Normal concentrations of the three main classes of immunoglobulins—IgG, IgM and IgA—were present in the serum. The syndrome has been confirmed in several additional cases. A strikingly high incidence of chronic superficial candidiasis has been noted in these children. In regard to susceptibility to *Candida* infection,[30] this syndrome, in which a thymic abnormality is the central defect, contrasts with Bruton-type agammaglobulinemia in the same manner as Swiss-type agammaglobulinemia contrasts with the Bruton type.

Congenital Absence of Thymus and Parathyroid Glands (III-IV Branchial Pouch Syndrome)

The ontogeny* of the parathyroid glands is from the third and fourth branchial pouches; the thymus arises from *Anlagen* in the third branchial pouches. An abnormality in the development of these embryologically closely associated organs results in the syndrome of congenital absence of the thymus and parathyroid glands.[32,33] Children with this syndrome exhibit tetany soon after birth, and hypocalcemia with hyperphosphatemia underlies the clinical manifestations. If lymphopenia is not present at birth, it develops in a progressive manner during the first year of life. Immunoglobulins appear in the serum in a normal sequence and reach normal concentrations.

That children with this syndrome are not necessarily lymphopenic at birth[34] is an interesting phenomenon which seems to contrast with the severe lymphopenia of Swiss-type agammaglobulinemia. Several possible explanations for this discrepancy can be given. Children with the III-IV branchial pouch syndrome come to the attention of clinicians soon after birth, primarily because of the tetany. On the other hand, children with Swiss-type agammaglobulinemia usually receive medical attention several months after birth, because of infection. It is conceivable that the lymphocyte counts initially are normal in both syndromes, but this has not been tested in Swiss-type agammaglobulinemia. Another possibility is that the presence of an epithelial rudimentary thymus in Swiss-type agammaglobulinemia has a suppressing influence on the proliferation of lymphocytes in other sites such as the bone marrow. The lymphocytes of children with the III-IV branchial pouch syndrome are abnormal when tested in vitro for their capability to respond by blast transformation to phytohemagglutinin and various antigens.[34] This may be taken as evidence that lymphocytes of children with this syndrome do not have the potential to express delayed-type hypersensitivity.

According to DiGeorge,[32] children with the III-IV branchial pouch syndrome are unusually susceptible to *Candida* infections. The three syndromes—thymic dysplasia with agammaglobulinemia, thymic dysplasia without agammaglobulinemia, and III-IV branchial pouch syndrome—have in common the absence of capability to react by delayed-type hypersensitivity and a susceptibility to candidiasis. Although in the latter two syndromes the serum immunoglobulin levels are normal, in all three syndromes there is a serious defect in the production of functional antibody. Therefore it is difficult to attribute the susceptibility to candidiasis to the absence of delayed-type hypersensitivity capability per se, because the sus-

*See Test Your Word Score, Page 45.

ceptibility may be a result of combined defects in delayed-type hypersensitivity and antibody formation. But absence of antibody formation alone, as occurs in Bruton-type agammaglobulinemia, does not predispose to candidiasis.

In another syndrome, ataxia-telangiectasia,[27] in which there is also a developmental abnormality of the thymus, usually low levels or absence of serum IgA, and relatively normal production of specific antibody, *Candida* infection has not been reported to our knowledge. The issue is confused, however, by the fact that the thymus is arrested in a somewhat later stage of development than is the case in the two previously discussed syndromes of thymic dysplasia.[27] Also, there is not the degree of lymphopenia which is seen in the three syndromes described above, although mechanisms of delayed-type hypersensitivity are abnormal in ataxia-telangiectasia. Clinical observations suggest a relationship between severely altered mechanisms of delayed-type hypersensitivity and susceptibility to candidiasis, with the possibility that combined abnormalities of cellular (lymphocytes and possibly granulocytes) and humoral (antibodies) mechanisms are prerequisites for the development of the infection and its progression.

Conditions without Known Underlying Abnormalities

Candida Granuloma

This disease is primarily encountered in children who, when afflicted, have a characteristic appearance.[35] The mucosa of the oral cavity is almost invariably infected with *Candida,* but the striking abnormality is the hyperkeratosis about the face and scalp. There is a chronic granulomatous reaction and, in typical cases, large horny masses develop at the involved skin sites. Biopsy of the skin lesions reveals typical granulomas with lymphocytic infiltration; in severe cases, giant cells may be found. This reaction is in sharp contrast to the indolent infection which is seen in patients with thymic agenesis or thymic dysplasia. In several instances, skin testing with *Candida* antigen resulted in a strongly positive delayed-type hypersensitivity reaction.[35] In other cases, no such reaction could be elicited.[36] It is not always certain, however, from the descriptions given that the patients who were classified as having *Candida* granuloma were representative of the same clinical entity. Skin biopsy is probably needed to make the distinction between milder forms of *Candida* granuloma and idiopathic chronic mucocutaneous candidiasis without granuloma.

The presence of a strongly positive skin test in *Candida* granuloma suggests that other mechanisms that may be important in the defense against *Candida* infections are lacking. Several serum factors, not identifiable as recognized classes of antibody, inhibit growth of *C. albicans* in serum. The anti-*Candida* serum factors have been discussed by Louria.[37] Another possibility is that mechanisms of delayed-type hypersensitivity proceed normally morphologically; but functionally they proceed only up to the point of eradication of the invading *Candida* organisms which persist among the accumulated lymphoid cells, epithelioid cells, giant cells, and macrophages.

Idiopathic Chronic Localized Mucocutaneous Candidiasis without Granuloma

In this condition the infection behaves in an indolent manner, which is the main distinguishing feature justifying its separate classification from *Candida* granuloma. The lesions of the oral cavity, the perlèche,* and the involvement of fingernails are in no way different from what is seen in the endocrinopathies and the immunologic deficiency syndromes discussed above. Similarly, the infection has its onset in childhood. Careful studies and follow-up of these patients into early adulthood are needed to rule out the existence of one of the primary endocrinopathies or its development later on. The diagnosis of this entity can be made with certainty only if the patient has reached the third decade of life without having developed primary hypoparathyroidism or primary Addison's disease. The literature contains a number of well-documented examples of this poorly understood disease; in two recent studies it was found that patients with this syndrome failed to react with the dermal manifestations of delayed-type hypersensitivity; but their lymphocytes could be transformed with phytohem-

*See Test Your Word Score, Page 45.

agglutinin in vitro.[38,39] Members of our group[40] have recently independently studied a similar patient, a 25-year-old man who had almost life-long mucocutaneous candidiasis without underlying primary hypoparathyroidism or primary Addison's disease. This patient was found to be unresponsive by cutaneous delayed-type hypersensitivity to *Candida* and a number of other antigens. The failure to respond by delayed reaction extended to mumps antigen and streptodornase-streptokinase, to which the patient had immediate reactions indicating the presence of specific antibody and the occurrence of previous exposure. The absence of delayed-type hypersensitivity to these three antigens was therefore abnormal. The patient was also found to have an aminoaciduria involving 13 amino acids, and there were abnormalities in the concentrations of various amino acids in the serum. Aminoaciduria was found once before at this clinic in a patient with chronic superficial candidiasis, but in our experience this is not a common finding in association with candidiasis. Most likely the combination of chronic mucocutaneous candidiasis, absence of delayed-type hypersensitivity, and aminoaciduria represents a separate and new entity.

Chronic Diffuse Candidiasis

Lehner[1,13] emphasized the existence of an entity of severe, extensive, progressive candidiasis of the skin. The oral mucosa and nails are usually infected, too. It has been described in at least eight men, and it usually occurs in adulthood. There was no evidence of underlying endocrinopathy of parathyroid or adrenal glands; nor was there an underlying malignant disease. The immunologic state has not been studied in patients of this group and they possibly are heterogeneous.

TABLE

Classification of Chronic Mucocutaneous Candidiasis

- A. Familial juvenile hypoparathyroidism, hypoadrenocorticism, and chronic mucocutaneous candidiasis
- B. Conditions with congenital abnormalities of the thymus:
  1. Thymic dysplasia with agammaglobulinemia (Swiss-type agammaglobulinemia)
  2. Thymic dysplasia without agammaglobulinemia (Nezelof-Allibone syndrome)
  3. Congenital absence of the thymus and parathyroid glands (III-IV branchial pouch syndrome)
- C. Conditions without known underlying abnormalities:
  1. *Candida* granuloma (chronic localized mucocutaneous candidiasis)
  2. Idiopathic chronic localized mucocutaneous candidiasis without granuloma
  3. Chronic diffuse candidiasis

Summary

Various clinical, endocrinologic, and immunologic aspects of chronic mucocutaneous candidiasis are reviewed. The wide spectrum of pathologic conditions which may be associated in patients who have primary hypoparathyroidism or primary Addison's disease with chronic superficial candidiasis constitutes one of the most intriguing facets of human disease. The most commonly encountered immunologic abnormality in nonendocrine candidiasis is absence of the capability to react by delayed-type hypersensitivity. This abnormality also occurs in the syndromes of thymic dysplasia with agammaglobulinemia, thymic dysplasia without agammaglobulinemia, and congenital absence of the thymus and parathyroid glands. Absence of delayed-type hypersensitivity is also a feature in at least some patients with idiopathic chronic mucocutaneous candidiasis. A new entity, chronic mucocutaneous candidiasis, absence of delayed-type hypersensitivity-aminoaciduria, is briefly described.

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When I rest I rust.—Fritz Thyssen

Neurological Grand Rounds

Occult Hydrocephalus

I am a very foolish fond old man
Fourscore and upward, not an hour more or less;
And, to deal plainly,
I fear I am not in my perfect mind.
Methinks I should know you, and know this man;
Yet I am doubtful; for I am mainly ignorant
What place this is; and all the skill I have
Remembers not these garments; nor I know not
Where I did lodge last night. Do not laugh at me.

King Lear
Act IV, Scene VII

SHAKESPEARE'S KING LEAR thus described the disorder under discussion as well as any modern writer. In the above quotation, one sees the agony of the aging mind. This "aging" produces a state of dementia. The association of dementia and hydrocephalus has received considerable attention in recent years.

Although Vesalius described the physical appearance of hydrocephalus in the sixteenth century, it was not until the early days of the nineteenth century that the studies by Dandy and Blackfair gave any indication as to the cause of the malady. It was their contention that the problem rose because of obstruction to the flow of the cerebrospinal fluid.[10] In children, accumulated cerebrospinal fluid produces pressure within the skull and forces the head to enlarge. Usually brain tissue is compromised. If the fluid accumulates after the closing of the sutures of the cranial vault, pressure symptoms of headache, nausea, vomiting, weakness and papilledema may be produced. Nevertheless, a relative increase in the amount of cerebrospinal fluid within the cranium has occurred without any overt signs of craniomegaly or pressure symptoms.[16] This situation is perhaps more correctly described as hydranencephaly* or occult hydrocephalus.

There are several types of hydranencephaly and to understand the anatomical findings in these cases, it is helpful to trace the circulation of cerebrospinal fluid within the central nervous system. Theories of the origin and absorption of cerebrospinal fluid were expounded by Eade[15] in the early 1900s. The flow of spinal fluid through the ventricular and subarachnoid spaces can be followed with radioactive elements.[5]

Based on recent studies, it is thought that cerebrospinal fluid is a transudate produced by the intraventricular choroid plexus, that it circulates in a well-

*See Test Your Word Score, Page 45.

defined route from the lateral ventricles, through the foramen of Munro, and joins the cerebrospinal fluid produced within the third ventricle. The mixture also eventually flows out of the third ventricle through the aqueduct of Sylvius where it joins cerebrospinal fluid produced in the fourth ventricle, which communicates with the subarachnoid space through the two foramina of Luschka and the foramen of Magendie. The cerebrospinal fluid reaches the spinal subarachnoid space and fills the cistern at the base of the skull. A small amount may travel a short distance down the spinal canal. The flow will then pass into fissures and sulci over the cortex where it is reabsorbed into the venous sinuses by way of their arachnoid villi.

Factors influencing this sequential flow include pressure of the active secretion of cerebrospinal fluid, pulsations of the intracranial arteries, and the action of the ependymal cilia. Lymphatics around the spine and cranial nerves as they leave the nervous system may also participate in reabsorption.[9]

Obstruction to Flow of Cerebrospinal Fluid

An obstruction at the foramen of Munro would cause unilateral dilatation of one of the lateral ventricles; there would be pressure and atrophy in the brain on the side involved and symptoms arising there from this condition are occasionally seen with cystic tumors of the third ventricle.

Caudal End of Third Ventricle

An obstruction which causes blockage at the caudal end of the third ventricle or the aqueduct would cause dilatation of the third ventricle and both lateral ventricles. This situation commonly exists in aqueductal stenosis or progressive stenosis from an inflammatory reaction after meningitis or encephalitis. Tumors in this area may cause an intermittent obstruction by acting as a ball valve.

Tumor Within Fourth Ventricle

A tumor within the fourth ventricle, e.g., a medulloblastoma seen in childhood or a pontine or cerebellar tumor in adults, may cause displacement or obstruction. The lateral ventricles, the third ventricle and the aqueduct of Sylvius would dilate.

Blockage of Foramina of Luschka and Magendie

Spinal fluid flows from the ventricular system into the arachnoid space through the foramina of Luschka and Magendie. These may be blocked by abnormal bone development, by herniation of the cerebellum through the foramen magnum or by chronic adhesions. In these conditions, the lateral, third and fourth ventricles would be dilated. Any of these disease processes would prevent the outflow of cerebrospinal fluid into the subarachnoid space. Dye injected into the ventricular system in the above conditions cannot communicate across the area of obstruction to the more distal or proximal parts of the system. For this reason, these examples are generally known as obstructive hydrocephalus.[10,15]

Fibrosis of Basal Cistern

The flow of cerebrospinal fluid may be blocked in other places as well. Fibrosis of the basal cistern would prevent flow of fluid forward and upward.

Clinically this may be seen in tuberculoma, leptomeningitis, aneurysms, hemorrhage, postoperative hematoma, arteriovenous malformation and parasitic infections. There is dilatation of the ventricles proximal to the obstruction, and a free communication with the subarachnoid space is observed.

Delay in Absorption

Another process that may cause a relative obstruction in the flow of cerebrospinal fluid is a delay or block in the absorption of the fluid. Experimentally this may be produced by the introduction of chemicals such as Thorotrast, India ink, or kaolin in colloidal suspension. Fibrosis of the arachnoid villi is seen in some of the cases where there has been blood within the subarachnoid space, as would occur with a subarachnoid hemorrhage or postoperatively.[6,15]

Overproduction

Overproduction of cerebrospinal fluid on an absolute basis could also cause a generalized hydrocephalus. Free communication between the ventricular system and the subarachnoid space is present, and for this reason it is known as communicating hydrocephalus.

Because of limited space within the cranial vault, a steady input of fluid which cannot escape would produce a considerably increased pressure, the amount of which would depend upon the ability of the choroid plexus to produce cerebrospinal fluid against a pressure diffusion gradient and the amount of leakage that may occur around the block. Actually, as the pressure within the cranium increases, the amount of absorption of cerebrospinal fluid may actually decrease because of pressure occlusion of veins.[17] Decreased venous run-off results in decreased flow and osmotic pressures to absorb the spinal fluid. Hydrocephalus in the adult may be associated with tumors of the third ventricle. In two such cases presented by Riddoch[16] in 1936, pressures of the lumbar subarachnoid space were normal.

Symptoms

The symptoms of hydrocephalus may vary from almost no mental impairment in some patients to almost complete dementia in others. The application of Pascal's principle helps one understand this variability.[1,2,11] The total force exerted on the wall of a closed container will depend on the pressure present and the area of the wall. The force on the walls would be greater in the places where the surface is exposed to the greatest pressure. Applied to the ventricular system, it can help explain the greater dilatation seen in the frontal poles and the lateral ventricles in the hydrocephalic.

Incontinence and Paraparesis

Symptoms in the hydrocephalic, however, depend upon the total amount and the site of brain atrophy. These include incontinence, paraparesis,[18] dementia, apraxia,[1,2] Parkinson-like syndromes[14] and akinetic mutism.[12,13] Presence of incontinence and paraparesis is felt to be due to the stretching of the long fiber tracks which traverse the ventricles from the frontal lobes. The pyramidal leg fibers would be the most displaced and suffer the brunt of local pressure atrophy.[18] Penfield and Elvidge contend that the marked degeneration of the nerve fibers to the bladder and leg in patients with hydrocephalus is due to local tissue ischemia from pressure on vessels feeding

that area. Other possible mechanisms include pressure of the brain stem against the clivus or pressure of the cortex against the calvarium.[18] Perhaps dementia and gait disturbance in hydrocephalus are due to similar disturbances. The poles of the ventricles are most subject to distortion.[1,18] The critical mass of frontal lobe tissue and the connection of the frontal cortex via the corpus callosum may be functionally or even anatomically disrupted.[12] In patients described by Riddoch[16] in 1936, there is early documentation of this problem. It is of interest that the cerebrospinal fluid in these patients showed normal pressure.

Inappropriate Action

Patients may show inappropriate actions, loss of tact and tenacity, Parkinson-like rigidity in facial movements and bradykinesia, due perhaps to pressure upon the basal ganglion which encroaches upon the ventricular system. Recently Messert[14] and also Adams[2] have described the occurrence of akinetic mutism with hydrocephalus. These patients are described as having a global apraxia and as sleeping more than normally. They are easily aroused, however. They make no sound but their eyes will regard the observer steadily or follow the movements of objects or the direction of sounds. There is no spontaneous speech and there is an apractic gait. They appear not to know where to put the feet. Messert felt that the symptoms were attributable to a disruption of motor and sensory tracts. There may also be electroencephalographic changes.[1,2,11,12] In the majority of these cases, small paroxysmal waves were observed in the frontal regions. There is also disruption of the normal alpha pattern.

Normotensive Hydrocephalus

This so-called normotensive hydrocephalus is a syndrome which has come under considerable scrutiny within the past four years.

Mental Deterioration

Adams et al., in 1965, presented three adults with a history of mental deterioration. These patients had several characteristics in common. The course of the disease was slow. The patients were all noted to have nystagmus. There was slowness of thought, impaired memory, incontinence of urine, and a slight elevation or normal cerebrospinal fluid pressure. An electroencephalogram showed diffuse theta or delta waves. These patients had pneumoencephalograms which showed dilated ventricles in the presence of adequate communication between the subarachnoid space; however, there was a failure of the air to pass over the cortex of the brain. Angiography showed an elevation of the anterior cerebral artery, suggesting the presence of pressure displacement; no atrophy to suggest "hydrocephalus ex vacuo" was found. After ventricular shunting, all three of the patients had remarkable improvement of symptoms.

Comments

One may ask: Can hydrocephalus exist without increased intracranial pressure? Referring to Pascal's principle, there is perhaps more significance in the force exerted by the fluid and the fact that this force is dependent on the area as well as on the pressure of the fluid. There may be a critical force that the brain can tolerate, which may be reached before marked pressure

increases are observed. Hakin claims that there is perhaps an initial elevation of the pressure which has caused structural damage and that this pressure has subsequently been compensated for. However, the force has increased enough to become symptomatic. It is possible that secondary methods of reabsorption may operate belatedly and may compensate for the obstruction to normal cerebrospinal fluid flow.

At this time there is no clear idea of the etiology; for this reason the syndrome at present is controversial. There have been several suggestions; Hakin[1,2] proposes that the pressure is aggravated by the intermittent elevation of an arterial pressure and pulsation. There is some evidence that hypertension causes an elongation and tortuosity of the basilar artery.[4] Displacement of the artery occurs into the cisterns and therefore causes a block in the flow of spinal fluid. Tumors have been described within the third and fourth ventricles, as well as in the cerebellum, which have been associated with the symptom complex.[13,16] The other causes of communicating hydrocephalus mentioned previously have also been suggested as causes of this syndrome.

The diagnosis of the communicating hydrocephalus depends on radiographic demonstration of dilatation of the ventricle with the air passing freely into the ventricular systems from the subarachnoid space. No definite structural lesion may coexist. The pneumoencephalograms also show little, if any, air over the cortex. The basal cisterns, pericallosal cisterns and often the ambient cisterns tend to be enlarged. The pericallosal artery and the anterior cerebral artery will demonstrate an upper displacement.[1,2,11] Isotope myeloencephalography may be useful.[3,5,11] Isotopically-labeled albumin is introduced into the subarachnoid space and, in a normal situation, the isotope can be demonstrated to be in the basal cisterns after one hour; by 12 to 24 hours it should be in the superior longitudinal sinus. By 48 hours, the activity should be diminished in the brain much more than expected by the natural decay of the isotope. In the normal situation, none of the isotope should be noted in the ventricular systems. In the case of the communicating hydrocephalus, the isotope is seen to collect in the basal cisterns, thalamus and the ventricular areas.

The nature of the disease process may be inferred from this information. If the problem were one of absorption alone, then we might expect dilatation of the sulci or pathways to the subarachnoid granulations. This has not been observed on the pneumoencephalogram; however, if air were blocked from passing into these areas, one would not expect to see them anyway. Pathologic studies have failed to show marked dilatation of these sulci.[13] The isotopic method also revealed that there is at least a functional block above the basal cisterns.

The treatment of occult hydrocephalus is the same as the treatment of any communicating hydrocephalus; a shunt relieves the pressure, and the patient's symptoms often subside rather dramatically, as was first demonstrated by Foltz and Ward[6] when they did ventriculomastoid shunting. Repeated lumbar punctures have shown a similar spontaneous recovery with the removal of spinal fluid.[1] Shunts have been placed to the peritoneum and the venous system. Some surgeons have measured the ventricular pressures and found them increased at the time of operation even though the lumbar subarachnoid pressures have been noted to be normal or low.[4]

Better ways to diagnose communicating hydrocephalus by history, physical examination or laboratory examinations are needed to aid in the differential

diagnosis of dementia. Other conditions to be considered include severe cerebral vascular disease, syphilitc dementia, torulosis,* alcoholic dementia subdural hematoma, Korsakof's dementia, brain tumor, Pick's disease, inclusion body encephalitis and hypercapnia.

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*See Test Your Word Score, Page 45.
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Conservatism and Medicine

Most physicians tend to think of computers in medicine as having a "far out into the wild blue yonder" aspect. To some this is stimulating; however, many persons tend to resent things which are hard to understand and the normal reaction is one of conservatism. . . . As understanding and experience improve, physicians can move from conservatism to active use of these splendid instruments in the practice of medicine.*

*A. H. Schwichtenberg in Richard Magraw: Ferment in Medicine, 1966.

Empty Promise

A doctor was examining a man at the end of a first-aid course. "Suppose," he asked, "there had been a car accident and you found a man bleeding profusely in the arm. What would you do?"

"I'd give him some brandy," answered the man.

The doctor, wishing to give him a second chance, said, "And what if you hadn't any?"

The man thought a moment. "Then I'd promise him some."*

*Maxwell Droke: The Speaker's Handbook of Humor.

Physician's Work Shop

Cystic Duct Cholangiography

A Simplified Procedure

The case for routine cystic duct cholangiography, performed during the course of all cholecystectomies, has been eloquently documented. A few of the compelling advantages cited by Jolly et al. include the following:

(1) A negative cholangiogram proved more accurate in excluding common duct stones than a negative choledochotomy.

(2) Unnecessary choledochotomies were avoided.

(3) Positive cystic duct cholangiography increased the yield of choledochotomy to 78 per cent.

(4) Unsuspected common duct stones were found in 6.3 per cent of all patients who had a cystic duct cholangiogram, but none of the usual criteria for choledochotomy.

(5) Visualization of the distal common duct and passage of dye into the duodenum was consistently obtained by cystic duct cholangiography. Instrumentation of the common duct often results in sphincter spasm and failure of dye to pass through to the duodenum during operative T-tube cholangiography.

(6) Routine cystic duct cholangiography provides a permanent record of the operative status of the extra hepatic biliary ducts.

Despite this, many surgeons do not employ this technique routinely with cholecystectomy. The above authors note that only 18 per cent of 286 members of the American Surgical Association, responding to a questionnaire, routinely employ cystic duct cholangiography. Other surgeons probably use it with no greater frequency. The greatest impediment to general acceptance of this procedure seemed to us to be the technical difficulties involved in catheterizing and securing a catheter in the cystic duct. We feel the following method overcomes these problems by allowing rapid and secure cannulation of the cystic duct.

Procedure

Materials

The necessary materials, aside from the basic x-ray equipment, are standard, inexpensive, and readily available. These include a 19-gauge disposable scalp vein needle*, two disposable 10-ml. or 20-ml. syringes (plastic disposable syringes are more satisfactory than glass because they do not stick when bloody), and hemostatic clips (Weck) of tantalum.†

A Bucky with cassette is positioned under each patient prior to the operative procedure. The location of the cassette is marked with two pieces

*Butterfly Infusion Set ™ - 19: Abbott Laboratories, North Chicago, Illinois 60064.
†Hemoclips: Edward Weck and Company, Inc., 49-33 31 Place, Long Island City, New York.

of tape to insure proper placement of additional cassettes for subsequent exposures. Portable x-ray equipment is employed. Control films are not routinely obtained.

Isolation of Cystic Duct

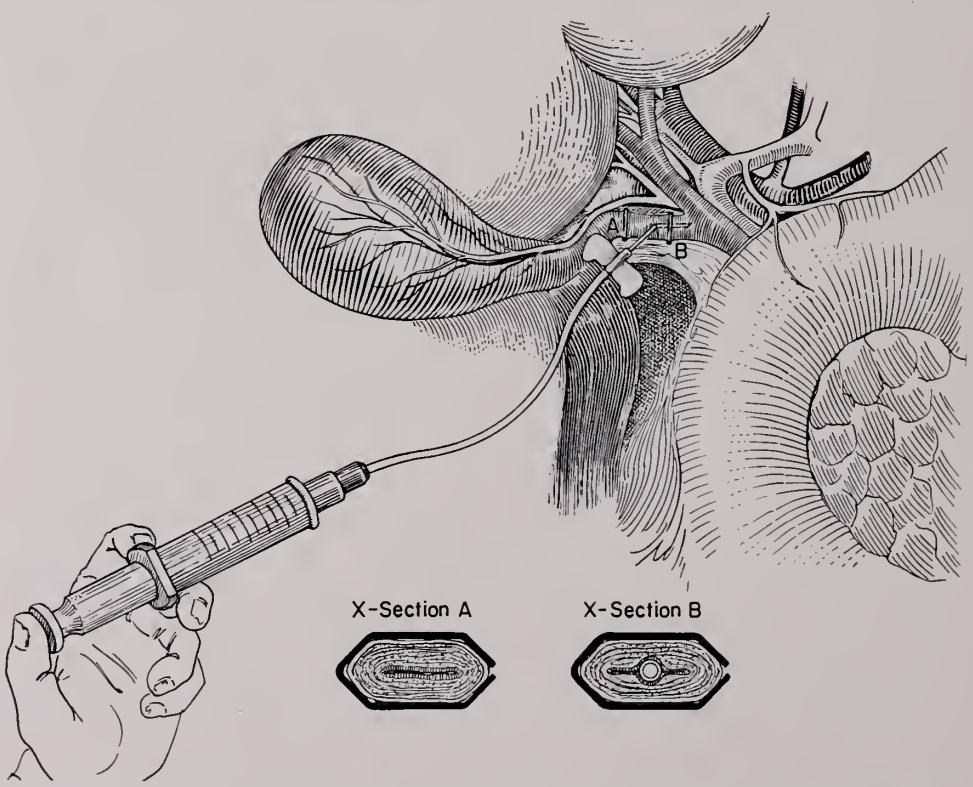
After the abdomen has been entered and explored, the cystic duct is isolated and clamped distally with a hemoclip to prevent back flow of the contrast material, and to protect against proximal migration of small stones.

Injection Into Cystic Duct

A saline-filled syringe is attached to the scalp-vein needle, and the tubing and needle are filled with saline. The 19-gauge scalp-vein needle is then bent to an angle of 20° with a needle holder and the needle introduced into the cystic duct. The needle readily overcomes any resistance which might be present from the spiral valves of Heister. Bile will flow into the plastic tubing connected to the needle indicating proper placement. Another hemoclip is then placed transversly across the cystic duct and the intraluminal portion of the needle, securely anchoring it in the cystic duct for the injection of the dye. Six milliliters of 50-per-cent hypaque is injected slowly and an exposure obtained with the patient apneic. An additional exposure is obtained after injection of six to ten more milliliters of dye. While the films are being developed, cholecystectomy is performed. The hemo clip will hold the needle securely in the cystic duct during these manipulations.

Concluding Comments

After satisfactory cholangiograms have been returned, the needle is re-



Figure—Cystic Duct Cholangiography: (A.) Hemoclip occluding cystic duct distally. (B.) Hemoclip securing scalp vein needle in cystic duct.

moved, the cystic duct ligated, and the operation completed.

We have employed this technique routinely with cholecystectomies in several St. Paul community hospitals. Even with differing operating room and x-ray personnel, we have found that it is quickly and reliably accomplished.

John F. Alden, M.D., F.A.C.S.
James W. LaFave, M.D., F.A.C.S.
St. Paul, Minnesota

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Shakespeare's Doctors

Dr. Butts

Henry VIII's physician, Dr. Butts, appears in no professional role in the play "Henry VIII." Instead, we see him acting only as loyal political henchman to the King: just happening, either by chance or contrivance, to be in the right place at the right time to observe the Archbishop of Canterbury, Cranmer, demeaned by the councilors: an indignity Butts later reports to the King.

That Dr. Butts was not a fictional character, however, but a licensed M.D. we learn from Goodall's Epistle Dedicatory: "Dr. William Butte, Fellow of Gonville Hall, in Cambridge, and Physician to King Henry VIII, was, Anno Domini 1529, admitted into the College of Physicians. Upon which he was required to subscribe to the due observation of the Statutes of the College, and to give his promise to use his best endowments for advancing the honour and perpetuity thereof."

Note: Shakespeare's slight change in the spelling of the doctor's name is defensible on grounds of poetic license.

John P. Wendland, M.D.

The cover slide was taken by Dr. Wendland after a fresh snow fall on the Upper Peninsula of Michigan during a skiing holiday.

Dr. Wendland is an ophthalmologist practicing in Edina and in addition is a professor of ophthalmology in the Medical School at the University of Minnesota. He is very active in the Minneapolis Cine Club and has produced several motion picture films on skiing.

Mrs. Wendland is the skier shown on the cover.

Work

One machine can do the work of fifty ordinary men. No machine can do the work of one extraordinary man.—Elbert Hubbard

Writers

An author departs; he does not die.—Dinah Mulock

Meetings and Announcements

American Board of Family Practice

The American Board of Family Practice announces that it will give its FIRST examination for certification in various centers throughout the United States. The examination will be over a two-day period on February 28-March 1, 1970. Information regarding the examination and eligibility for the examination can be obtained by writing: Nicholas J. Pisacano, M.D., Secretary, University of Kentucky Medical Center, Annex #2, Room 229, Lexington, Kentucky 40506.

Clinical Neurology Fellowships

Fellowships in Clinical Neurology have been established at the Minneapolis Veterans Administration Hospital.

General Practitioners and Non-Neurological Specialists are invited to apply for an intensive postgraduate training experience on the Neurological Wards at the Minneapolis VA Hospital. Programs are designed to provide one to four weeks of supervised bedside and didactic instruction in the diagnosis and treatment of neurological disease. Those accepted for the fellowship may receive quarters, if desired. Fellows may elect any one or a combination of the following programs:

Week 1—The Neurological Examination
Week 2—Special Neurological Diagnostic Procedures
Week 3—Latest Treatments of Acute and Chronic Neurological Problems
Week 4—Frontiers of Neurological Research

Each program will commence on Monday and terminate on Friday.

Apply to Milton Alter, M.D., Ph.D., Chief, Neurology Service, Veterans Administration Hospital, 54th St. and 48th Ave. So., Minneapolis, Minnesota 55417.

Minnesota Heart Association

Heart symposium, Saturday and Sunday, January 24-25, sponsored by the Minnesota Heart Association at the St. Paul Hilton Hotel, St. Paul, Minnesota. Topic: What To Do About High Blood Pressure? Chairman: Kenneth G. Berge, M.D.; Time: January 24th, 8:30 to 4:30 and January 25th, 9:00 to 12:00.

February Meetings

Hennepin County Academy of General Practice Chapter Meeting, February 16 at the Minneapolis Athletic Club.

Minnesota Academy of Occupational Medicine and Surgery, February 19th at the Minneapolis Club, 729 Second Avenue South, Minneapolis, Minnesota. Program Chairman: Edwin G. Benjamin, M.D.

The Winter Meeting of the Minnesota Radiological Society will be held at the Sheraton-Ritz Hotel in Minneapolis on February 7, 1970.

E. V. Allen Memorial Scholarships

Applications are now being accepted for the E. V. Allen Memorial Scholarships, open to junior and senior medical students attending medical schools in the United States or Canada. The scholarship provides three months of cardiovascular study at the Mayo Clinic, Rochester, as well as $1,000 award. Deadline for applications is April 1, 1970. Applicants will be notified by May 1, 1970. Brochures may be obtained by writing to Minnesota Heart Association, 4701 West 77th Street, Edina, Minnesota 55435.

Special Article

A Surgeon's Experience in Vietnam

RICHARD D. CHAPMAN, M.D.*
San Francisco, California

It is a dramatic event, especially at night, to hear the whir and chop-chop-chop of the helicopter as it swoops into the helipad. Stretcher bearers rush out into the wind of the rotor to unload the bandaged and splintered wounded and bring them into the bright lights of the receiving shed. It is the advent of the full utilization of helicopter evacuation that has hurried to the surgeon, injured patients who in previous wars would have died before treatment could be instituted. In Korea, World War II and earlier wars the ratio of wounded soldiers reaching treatment, compared to those dying before they could reach treatment, has been constant at 4:1. In Vietnam the ratio of injured reaching treatment has been increased to 5.2 for every soldier killed.[1] Despite this increased number of "mortally injured" reaching hospitals in Vietnam, the mortality rates for patients admitted to treatment facilities remain low: World War II, 4.5%; Korea, 2.5%; Vietnam, 2.3%.[1]

The People

The heat, the humidity, the stench of inadequate or nonexistent plumbing, and these strange little people staring from faces with emotionless smiles, or with no apparent faces at all as they scurry along hidden under their sampan straw hats, leads to the immediate feeling that identification with this new people is going to be completely impossible.

Time changes much of this as one meets more and more Vietnamese, especially the educated and business classes, and before long one learns to say, "Chau" ("Hello"), and with some effort to carry on rudimentary conversations. In fact, once a true friendship is established, the Vietnamese demonstrates a candidness and ingenuousness that belie our preconceived conceptions of the devious and calculating oriental personality.

The Medical-Surgical Environment

Physically and psychologically the surgeon in Vietnam operates under the most ideal circumstances in modern warfare. Although subject to surprise mortar attack any place and any time, the hospital environment is extremely stable; at no time has it been necessary to sacrifice patient care because of massive attack, bombardment or retreat. In previous wars, the greatest morale deterrent was the instability of the environment and of patient care. But not in Vietnam. On the contrary, the greatest deterrent to the morale of medical personnel and support troups arises from the extreme stability of the environment: the boredom due to close confinement in a never-changing, circumscribed compound-type of existence.

Battle lines as such do not exist in Vietnam; therefore the successive echelon type of medical care and evacuation of patients does not fully apply as in previous wars. In such a more "typical" situation, life-saving surgery would be performed in forward Surgical Hospitals. Within 24 to 48 hours these patients would be sent back to larger, more permanent Evacuation Hospitals for secondary care. By contrast, in Vietnam all types of hospitals may and do receive their share of fresh, severe casualties. As most of the combat evacuation is controlled by radio from regional group commands, the number of most severely injured patients can be "spread out" among a number of Surgical Evacuation and Field Hosiptals in the area to prevent overload at any one point. My entire year was spent at the newly-opened 67th Evacuation Hospital in Qui Nhon in the Central High-

*Present address: Division of Vascular Surgery, Department of Surgery, University of California, School of Medicine, San Francisco, California.

lands, where casualties are received in a large, open frame and screen structure which can handle approximately 30 stretchers at a time (Figure 1).



Fig. 1—Patients are received on stretchers in an open frame and screen structure. Cutdowns and chest tubes are being inserted as blood is drawn for typing and cross matching.

Resuscitation

The receiving unit is geared to two procedures: resuscitation and triage.* Resuscitation consists of (1) venous cutdowns, often as many as four, (2) airways, including tracheostomies as indicated, (3) chest tube placement, (4) typing and cross-matching for blood transfusions, and (5) immediate infusion of Ringer's lactate solution until blood becomes available.

Triage in the classical sense is not used in Vietnam. Due to the relatively low and steady rate of casualties, the coordination of evacuations by area dispatch, and the widely dispersed facilities available, the most seriously wounded go directly to surgery and are not shunted aside to live or die on their own as might occur in very large mass casualty situations.

Triage in Vietnam consists of choosing which of the most seriously injured patients should go to the operating room first and selecting surgical teams and anesthetists for each patient. At the 67th, we averaged from six to eight fully trained surgeons, and the responsibility for "triage" was rotated daily throughout this group. We also had one to two orthopedic surgeons, two neurosurgeons, an ophthalmologist and an oral surgeon. From one to five partially trained surgeons were available to help the surgical and orthopedic teams.

After initial resuscitation, x-rays were taken in an adjacent quonset facility. Radiographic localization of missiles, estimation of missile tracts and evaluation of associated fractures is invaluable in planning surgical procedures and approaches and was never omitted except in patients requiring operating room resuscitation and immediate surgery. After x-ray, the patient was carried to an air-conditioned quonset preoperative ward and later to one of five air-conditioned operating rooms by his team of two surgeons and one anesthetist.

Surgical Teams

The multiple team approach was often utilized, with an orthopedic or another surgical team working on extremity wounds simultaneously, once the abdominal situation became stable. This multiple team approach cut down on anesthesia time in the individual patient as well as facilitating rapid turnover of the operating suites.

The following case illustrates the typical hospital procedure in the care of the acute casualty:

Case Report

A lieutenant, 22 years of age, was wounded by artillery fragments to the left abdomen while on forward patrol. A combat medic wrapped his eviscerated, bleeding bowel with field dressings and called for a Med-Evac helicopter. In a matter of minutes he arrived at the base camp aid station in shock. O-positive low titer blood was started through two Intracaths and the patient was replaced in the helicopter, unstable despite blood transfusions. He arrived at the 67th Evacuation Hospital within an hour of injury and was given his ninth unit of O-positive blood. His blood pressure was 60. He was incoherent and in deep shock.

Evaluation

Quick evaluation showed that the wounds were limited to the abdomen and left flank. His tag from the aid station read "Abdominal Wound-Evisceration. O-positive blood given, 8 units; medications: tetanus toxoid, penicillin 1.2 million units, streptomycin 1.0 gm."

Emergency Care

His Intracaths were quickly replaced with three large cutdowns, using intravenous tubings directly into his cephalic and basilic veins. More blood was given and an indwelling catheter placed in his bladder. Blood was drawn for type and cross match. However, since he had already received nine units of O-positive blood, O-positive blood was continued regardless of blood typing. The patient was on the operating table, bypassing x-ray, within minutes of arrival at the 67th Evacuation Hospital.

Operative Findings

As soon as the dressings were removed it became ap-

*See Test Your Word Score, Page 45.

parent that he was not only eviscerated anteriorly but posteriorly as well. His left side had been shot away, leaving a defect from the midline anteriorly and from the psoas muscle posteriorly and from the left costal margin above down to the pelvis, where his iliac wing had also been blown off (Figure 2).

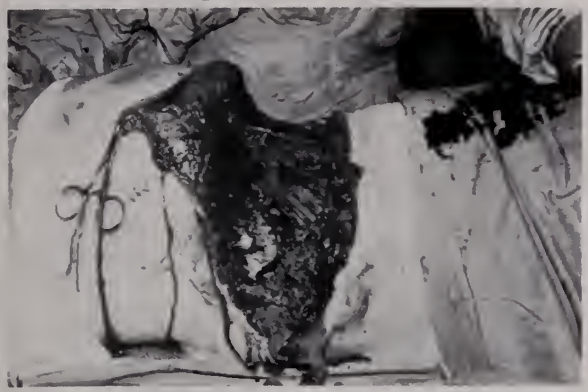


Fig. 2—View of large flank defect after abdominal closure. Patient is on his right side at the time of redressing the wound.

His left colon was missing, the small bowel was damaged and the mesentery was actively bleeding. A metal fragment the size of a fist lay against the left kidney which itself was literally balanced on the precipice of the open wound over the operating table below. A larger fragment must have gone completely through him. The quadratus muscle and the entire oblique group were missing on the left side.

Procedure

Hemostasis was achieved in the mesentery, and the bleeding pelvis and gluteal areas were temporarily packed. A transverse end colostomy and sigmoid mucous fistula were fashioned from the traumatically amputated bowel ends. The holes in the small bowel were oversewn and some areas resected. Peripheral areas of the wound and the pelvic area were then debrided of obvious necrotic tissue, and the remnant of the iliac bone was trimmed back. Closure was an innovation of the moment; heavy #3 silk was used to join the linea alba anteriorly down to the psoas muscle posteriorly. The ureter was pushed toward the midline off the psoas to accomplish this. The large flank space once in the domain of the abdomen and the remainder of the iliac bone were thus exteriorized from the intra-abdominal area, and this large defect was packed. Total blood given was 27 units.

The patient immediately went into shock in the recovery room; his blood pressure was 80 and he was bleeding steadily from his packed wounds. Clotting time was 32 minutes. Fresh blood arrived and six units were given to stabilize the patient. His wound stopped bleeding without significant hemostasis and was repacked. His condition remained stable. Clotting time was 12 minutes.

He had a febrile course, treated from the start with Colymycin and Keflin, and to our surprise developed no intra-abdominal abscess. He required a second minor debridement of the flank wound and iliac bone and subsequently underwent colostomy closure and skin grafting to the flank defect in a Stateside hospital (Figure 3).

Two years later he is walking normally and taking



Fig. 3—The same patient one year later, after multiple skin grafts and physical therapy.



Fig. 4—Entry wound in lower leg.



Fig. 5—Exit wound in same leg.



Fig 6—Incision necessary to explore adequately devitilized areas in the type of wound seen in Figures 4 and 5.

postgraduate courses in physics at a major university.

Soft Tissue Wounds[1,2]

Debridement is removal of all devitalized or contaminated tissue. This involves primarily muscle, but frayed fascia and damaged skin margins are also excised. Because of the high velocity of both carbine and fragment injuries in modern warfare and their resultant explosive and cavitation effects as they pass through solid tissue, the extent of damage exceeds any estimate of the superficial aspect of the wound.

Debridement

The entire wound tract must be exposed, and whatever incisions are required for that exposure must be utilized. Failures in wound debridement do not come from mistaking dead for live tissue but from failure to expose the tissue initially for evaluation.

Figure 4 shows an innocuous-appearing entry wound from a high velocity carbine round. Figure 5 shows the exit wound. Long incisions, often on each side of the extremity, are necessary to expose adequately for debridement (Figure 6).

Wound Care

After debridement, wounds are dressed with fine mesh gauze and occlusive bandages; tight packing is avoided to allow good drainage. All patients receive antibiotics. The patient is returned to the operating room after approximately five days. Closure with wire is performed at this time without any further manipulation of the wound unless small areas of devitalized tissue require removal before closure. Larger wounds may be only partially closed and skin-grafted. The patient may be evacuated to Japan for wound closure with grafts and pedicle flaps as required. Many of these patients then return to duty.

Hand Wounds

Even hand wounds are treated "open" in many hospitals in Vietnam. After proper debridement the hand is dressed and elevated. After 72 hours the patient is anesthetized, the hand inspected, and further minute trimming accomplished.

Pins are inserted for bone stabilization and the incision is closed or covered with skin grafts at the 72-hour period.

Burkhalter gives an excellent review of this method as practiced in Vietnam.[3]

Face Wounds

Preservation of tissue and primary repairs give optimal cosmetic results, with infection a rarity.

Neck Wounds

Soft tissue wounds in this area are treated with both immediate and delayed closures with equally good results. Tracheal injuries can usually be handled through the neck by mobilizing the carina by blunt dissection, though one case of tracheal transection required a sternal splitting incision to mobilize enough trachea and lung to permit repair.

Intracranial Injuries

All intracranial injuries were treated by our neurosurgeons. Other than the necessary hemostasis, debridement and dural closure, emphasis was placed on removal of all loose bone fragments as potential sources of abscess formation. Re-operations for retained bone fragments were not uncommon. Retained metal was felt to be more innocuous.

Chest Injuries

Almost all missile injuries involving the lungs respond well to large-bore chest tube suction. Thoracotomies are necessary to: (1) repair chest wall defects, (2) explore mediastinal and heart injuries, (3) perform lung resection if bleeding is not controlled by chest tubes alone, and (4) extend abdominal incisions when necessary, as in many liver injuries.

The so-called "wet lung" syndrome was seen on two occasions within one year at the 67th Evacuation Hospital. In the first case thoracic trauma was present; in the second, close proximity blast was the precipitating cause. "Wet lung" did not occur at our hospital from shock or overtransfusion alone, though each has been implicated as a cause in some patients.[4]

Intra-abdominal Injuries

All suspected intra-abdominal injuries are explored on the basis of (1) the location of the

penetrating wound, (2) x-ray localization of fragments, and (3) physical symptoms and signs.

Any penetrating wound from the 5th rib superiorly down to as low as the buttocks and perineum is in itself suggestive of intra-abdominal injury.

X-ray confirms the above suspicion, localizing fragments in borderline cases. Wounds as high as the shoulder and as low as the thigh can penetrate to the intraperitoneal area, depending on their force and direction. Intravenous pyelograms are invaluable in urinary tract injuries if only to ensure function in the opposite kidney prior to possible nephrectomy. Cystograms may uncover a bladder injury that is occasionally difficult to detect at surgery.

Peritoneal symptoms and signs are usually obvious and correlate with the external injury. In patients with no physical findings, the site of injury, the x-rays and suggestive signs become more important as determinants for operation. In fact, the absence of peritoneal signs is insignificant if the other suggestive signs are present.

Bowel Injury

Entrance-Exit Holes

If one counts the number of holes in the stomach or bowel after missile injury, one should have an even number for all the entry and the exit wounds. Odd numbers may indicate a tangential tear, which is uncommon, or an exit wound hidden in the mesentery of the bowel.

Stomach

Holes in the stomach are inverted, usually in two layers. Holes in the small bowel are simply inverted. Multiple holes in a confined area of small bowel and some difficult wounds along the mesenteric border are usually best resected with end-to-end intestinal anastomoses (Figure 7).

Colon-Rectum

Right colon wounds do well following right colectomy and primary ileotransverse colon anastomoses. However, other colon injuries are either exteriorized or resected with the resected ends brought out as end colostomies and mucous fistulae.

Rectal wounds require diligent exploration,



Fig. 7—Most holes in the small bowel are simply inverted. Multiple holes in close promixity as shown here require bowel resection with reanastomosis.

based on the missile tract as evaluated from the entry wound and x-rays. Small perforating rectal wounds are not easily demonstrated at laparotomy. If blood is found during sigmoidoscopy, a totally dividing colostomy is performed whether or not an actual perforation is found.

Liver Injuries

The most immediate problem in hepatic injuries is the life-saving control of hemorrhage. The non-bleeding, simple perforation or laceration may be simply drained.

Control Bleeding

Bleeding wounds may require: (1) spreading the wound to ligate bleeding vessels, (2) incising uninvolved liver to expose the bleeding wound tract and ligate bleeding vessels, or (3) resection of wedges, segments or lobes to control hemorrhage. Packing is not advised unless there is no alternative after resection.

The remaining principles of operative care of the injured liver are essentially prophylactic. First, prevention of late hemorrhage is a corollary to ligation of bleeding vessels and adequate resections while controlling the primary hemorrhage. Reliance on packing alone has been demonstrated in previous wars to lead to late hemorrhage as well as abscess formation.[5]

Prevent Infection

Second, the prevention and anticipation of postoperative abscess must be included in the initial care. Prevention consists of removing all liver substance which has been macerated or devascularized whenever possible and ligation of severed intrahepatic bile ducts with occasional common bile duct T-tube drainage to minimize bile leakage.

Other Abdominal Injuries

Splenic injuries are resected. Pancreatic injuries are resected or drained, depending on the severity of the lesion.

Macerated and badly fractured kidneys are usually removed. Lesser injuries often are only drained out the flank.

Vascular Injuries

The pathophysiology and management of vascular injuries as seen in the Vietnam casualties have been thoroughly reviewed by Whelan.[1]

Resection

Our surgical approach was identical in most cases and emphasized the resection of arteries at the site of injury, one centimeter in each direction to include blast injury not usually seen with the naked eye.

On several occasions extensive arterial injuries were observed with distal pulses present. I personally cared for two patients with fragment injuries near the clavicle with intact radial pulses. One patient had a large hematoma, one did not. Other patients had injuries which included not only arterial lacerations but arterial wall contusions; in three cases fragments were actually embedded in the arterial wall itself, but as yet had not led to thrombosis.

Arteriography

Arteriography would have demonstrated some of these injuries, but the main point here is that an artery located in the path of a suspected wound tract is a potentially damaged artery until proven otherwise. If the artery proves to be uninvolved, elective exposure is a benign procedure. If left alone, late hemorrhage, late thrombosis, arteriovenous fistula and false aneurysm are the sequelae. In my experience these complications can be more permanently disabling than initial resection and vein graft.

Case Report

Another case is that of a 20-year-old male with fragment wounds of his head, left eye, abdomen and all four extremities. After ten hours of surgery, including orthopedic care of his extremities, a laparotomy, a craniotomy and a left eye exenteration, there remained a minute, 2-mm perforation in the skin in the left neck over the anterior border of the sternocleidomastoid muscle. After ten hours there was absolutely no hematoma or swelling. A preoperative x-ray showed the tiny fragment at the level of the cervical transverse processes.

Figure 8 shows the laceration in the left common carotid artery with a surgically placed shunt in view. On exploration no hemorrhage occurred until the carotid sheath had been incised despite both anterior and posterior holes in the artery. A vein graft was used to replace this portion of the artery, and again our policy of exploring potential arterial injuries appeared to be correct.

Summary

The quality of medical care our Vietnam war casualties are receiving is probably better than that received by most civilian casualties in modern urban centers in the United States. Helicopters deliver patients to the receiving wards in Vietnam more rapidly than ambulances deliver patients injured on freeways to most American hospitals. Once in the hospital Vietnam casualties are resuscitated more vigorously and taken to the operating room sooner than would be possible in the average community hospital. Perhaps the perfection of these evacuation, resuscitation and treatment techniques and their subsequent application to the care of civilian trauma at home may constitute one of the plus values of the Vietnam war.

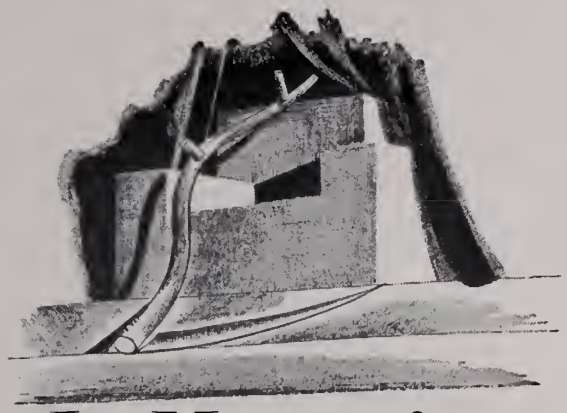


Fig. 8—Right common carotid arterial injury with a surgical shunt in place within the lumen. There were no signs of hemorrhage prior to exploration.

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A beard creates lice, not brains.—Ammianus



In Memoriam

Great men stand like solitary towers in the city of God.—Longfellow.

WILLIAM R. HEILIG, M.D.

Dr. William R. Heilig, 47, Twin Cities pediatrician, died November 18. He was chief of the Children's Seizure Clinic in the St. Paul Outpatient Medical Center and was a clinical assistant professor in the Department of Pediatrics at the University of Minnesota.

On the staffs at St. Joseph's St. Luke's, Midway, Children's, Miller, Mound's Park and Hennepin County General Hospital, Dr. Heilig was a member of the St. Paul Association for Retarded Children, the Minnesota Association for Brain Injury, the American Academy of Pediatrics, the Northwest Pediatrics Society, the Ramsey County Medical Society, the American Medical Association and the Minnesota State Medical Association. In addition he was a diplomate of the American Board of Pediatrics.

Surviving Dr. Heilig are his widow, two sons and two daughters.

FREDERICK J. VOLLMER, M.D.

Dr. Frederick J. Vollmer, 63, Winona ophthalmologist and otolaryngologist, died September 29. Born in Council Bluffs, Iowa, Dr. Vollmer obtained his medical degree at the Rush Medical College in Chicago. He interned at St. Barnabas Hospital in Minneapolis and did his postgraduate work at Rush Medical College.

Dr. Vollmer was a member of the Winona County Medical Society, the American Medical Association and the Minnesota State Medical Association.

PAUL R. GRONVALL, M.D.

Dr. Paul R. Gronvall, 71, Hopkins surgeon, died September 12. Born in Minneapolis, Dr. Gronvall attended the University of Minnesota Medical School where he obtained his degree in medicine. He interned at the Hennepin County General Hospital.

He was a fellow of the American College of Surgeons, a member of the Hennepin County Medical Society and the American Medical Association and an Associate Member of the Minnesota State Medical Association.

He is survived by his wife and two children.

CHARLES W. FOGARTY, M.D.

Dr. Charles W. Fogarty, Jr., 54, St. Paul physician, died November 20. A graduate of the University of Minnesota Medical School, Dr. Fogarty had a private practice in St. Paul, specializing in internal medicine. He was a lifetime resident of St. Paul.

Dr. Fogarty was a member of the Ramsey County Medical Society, the American Medical Association and the Arthritis and Rheumatism Foundation and an Associate Member of the Minnesota State Medical Association.

He is survived by his wife, four daughters and two sons.

GUSTAF THEODORE NORDIN, M.D.

Dr. Gustaf T. Nordin, 80, retired radiologist, died November 7, in Kaneohe, Hawaii. Born in Sweden, but educated at the University of Minnesota Medical School, Dr. Nordin interned at the Swedish Hospital in Minneapolis. His post-graduate work was done in Stockholm and Vienna.

He was a fellow of the American College of Radiology and a member of the Hennepin County Medical Society and American Medical Association. He was a 50 Club and Associate Member of the Minnesota State Medical Association.

Dr. Nordin is survived by his wife and two sons.

CHAUNCEY A. McKINLAY, M.D.

Dr. Chauncey A. McKinlay, 79, Minneapolis physician, and a former president and secretary of Blue Shield, died November 17. Born in Wichita, Kansas, Dr. McKinlay was a graduate of the Kansas University Medical School and served residencies at Yale University and the University of Minnesota Medical Schools.

A member of the staff of Northwest, Methodist and Ashbury Hospitals, Dr. McKinlay was active throughout his professional years in the Hennepin County and Minnesota State Medical Societies and was a member of the American Medical Association and the American Board of Internal Medicine. He was also a member of the American College of Physicians, the American College of Chest Physicians, Minneapolis and Minnesota Academies of Medicine and one of the earliest members of the Board of Blue Shield of Minnesota. Dr. McKinlay also served as a president of the Minnesota Tuberculosis Association.

He authored numerous medical publications and coauthored a two-volume book on diseases of the chest and heart.

Dr. McKinlay is survived by his wife and two sons, one of whom is Dr. Gordon L. McKinlay of Minneapolis.

WALTER H. FINK, M.D.

Dr. Walter H. Fink, 74, Minneapolis ophthalmologist, died December 5. An authority on the vertical muscles of the eye, Dr. Fink was an associate professor at the University of Minnesota. He had also authored a book involving the muscles of the eye.

Dr. Fink was a member of the Hennepin County Medical Society, the American Medical Association, the American Ophthalmology Society and a Life Member of the Minnesota State Medical Association.

He is survived by his wife, two daughters and two sons, one of whom is Dr. Robert J. Fink of Hopkins.

Medical Terms and Their Lay Synonyms

(Continued from December issue*)

Beer barrel—*abdomen*
Beet juice—*blood or uterine discharge*
Begma—*phlegm*
Bejel—*non venereal treponematosis*
Bellows—*abdomen*
Belly ache—*abdominal pain*
Belly bound—*constipated*
Belly button—*umbilicus*
Belly pull—*cesarean section*
Benders—*abdominal cramps*
Benders—*knees*
Beri beri—*vitamin B_1 deficiency*
Berries—*testicles*
Bezer—*nose or face*
Big belly—*abdominal distention*
Big head—*anthrax*
Big jaw—*actinomycosis*
Big one—*expulsion of feces*
Bigoo—*mouth or nose*
Bile house—*gallbladder*
Bile tank—*gallbladder*
Bilious—*hepatic dysfunction*
Bilious fever—*malaria*
Bilious remittent fever—*dengue*
Billard ball—*alopecia*
Bing—*hypodermic injection*
Bing spot—*vaccination scar*
Bird arm—*atrophic forearm*
Birdies—*nausea*
Birth dimple—*umbilicus*
Birth mark—*nevus*
Birthing—*delivery*
Bische—*dysentery*
Bishra boil—*oriental sore*
Bismuthitis—*syphilis*
Bite air—*gasp for air*
Bitter pill—*physician*
Blabber—*tongue*
Black and blue spots—*ecchymoses*
Black death—*pasturella pestis infection*
Black eyes—*amaurotic eyes*
Black fever—*kala azar*
Black fever—*Rocky mountain spotted fever*
Black leg—*anthrax*
Black pox—*variola*
Black tongue—*niacin deficiency*
Black vomit—*yellow fever*
Black water—*anthrax*
Black water fever—*malaria*
Blackeye—*orbital hemorrhage*
Bladder tea—*urine*
Bladding fever—*pemphigus*
Blasted event—*delivery*
Blattern—*variola*
Bleeders—*hemophiliacs*
Blessed event—*delivery*
Blind ear—*deaf*
Blind piles—*non bleeding hemorrhoids*
Blinds—*eyes*
Blister mechanic—*physician*
Blister on the lung—*emphysematous bleb*
Blood blister—*subcutaneous hematoma*
Blood flukes—*schistosomiasis*
Blood letting—*phlebotomy*
Blood poisoning—*septicemia*
Blood pus poisoning—*pyemia*
Blood pusher—*heart*
Blood spitting—*bronchial hemorrhage*
Blood stroke—*cerebral vascular accident*
Blood sucker—*physician*
Bloody flux—*dysentery*
Bloody tumor—*aneurysm*
Blotched face—*acne*
Blow a gasket—*cerebral hemorrhage*
Blow holes—*nostrils*
Blue baby—*tetralogy of Fallot*
Blue balls—*gonorrhea*
Blue birds—*sodium amytal tablets*
Blue boar—*venereal disease*
Blue disease—*cyanosis*
Blue heaven—*sodium amytal tablets*
Blue jack—*cholera*
Blue skin—*cyanosis*
Boco—*nose*
Body trouble—*gynecological disease*
Body wax—*feces*
Body wires—*nerve fibers*
Bold hives—*urticaria*
Bolus—*physician*
Bone adjuster—*osteopathic physician*
Bone bender—*physician*
Bone box—*cranium*
Bone breaker—*physician*
Bone factory—*hospital*
Bone house—*hospital*
Bone house—*human body*
Bone tumor—*actinomycosis*
Bonnet—*head*
Boo—*expulsion of feces*
Booby—*breast milk*
Boogie woogie—*secondary lues*
Boom—*expulsion of feces*
Booms—*elbows*
Bornholm's disease—*pleuradynia*
Born in a caul—*delivered within the amnionic sac*
Bot—*tuberculosis*
Bottle nose—*rhinophyma*
Bottle openers—*laxative tablets*
Bouquet—*dengue*
Bouquet—*nerve plexus*
Bow leg—*genu varum*
Bowel movement—*expulsion of feces*

*See page 1902.

Eugene Benet, M.D.†
Syracuse, New York

†Assistant Professor of Radiology, University of Syracuse Medical Center.

Even mild to moderate anxiety is often tinged with depression



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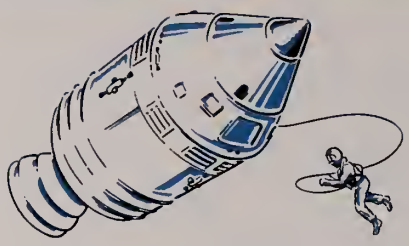
Precautions: There have been infrequent reports of leukopenia and/or agranulocytosis and convulsive seizures. In epileptic patients, anticonvulsant medication should also be maintained. Pigmentary retinopathy may be avoided by remaining within the recommended limits of dosage. Administer cautiously to patients participating in activities requiring complete mental alertness (e.g., driving). Orthostatic hypotension is more common in females than in males. Do not use epinephrine in treating drug-induced hypotension. Daily doses in excess of 300 mg. should be used only in severe neuropsychiatric conditions.

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Objectives and Compensations of the University Trained*

OWEN H. WANGENSTEEN, M.D.†

SINCE MEDIEVAL TIMES, universities have signalized granting of degrees as very special occasions. The only thing that has changed is that now you are asked to listen to a speech rather than to make one.

This is a new role for me. Men of my profession are commonly termed sawbones. Over my long years of tenure at the University and its Medical School my activity as a surgeon was essentially that of plumber of the alimentary tract. I have worked at both ends, but largely in between. Gaseous deflation has been my chief occupation. I must, therefore, not allow this effort to reflect evidence of extension by inflation.

In an address to the 166th Ohio Regiment, toward the end of the Civil War, Abraham Lincoln said:

"I happen temporarily to occupy this White House. I am a living witness that your children may look to come here as my father's child has."

So, too, I may say that in coming here before you now at the invitation of President Moos, I do so in a spirit of humility, welcoming the opportunity to say how much this University has done for me. The educative process which this University provided, together with Time and Associates, raised the sights of a farm boy with hands heavily calloused from hard work to attempt to make something of himself. So too, I am certain, has our University done for many of you. If each of you will concern yourself more over making something *of* yourself than *for* yourself, you will be happier and the mission of the University in helping you discover yourself will have been achieved. This, I feel, is the chief function and responsibility of Institutions of Higher Learning and should be the primary aim of the educative process. Every man has talents unknown even to himself. Great Teachers, through exciting students' interests, lead them on and communicate their own contagious enthusiasm for learning. In responding to the challenge, spirited students summon all their energy to activate their latent talents, thus reaching beyond what they had thought themselves capable of doing.

Ideas and knowledge are still the most unexplored areas of the world. Men and women who dedicate themselves to unsolved problems will find they have become their own best teachers. Almost two centuries ago Edward Gibbon, noted historian, said, "Every man who rises above the common level has received two educations: the first from his teachers; the second, more personal and important, from himself—he cannot forget the era of his life in which his mind expanded to its proper form and dimensions."

More Important Roles for Women

In the decades ahead, I believe we may look to a more active participation

*Presented at the University of Minnesota Commencement, August 23, 1968.

†Regents' Professor of Surgery, University of Minnesota.

by women in the competitive learning process. I was brought up in the Country School Spelling Bee era, and it always mystified me why, as our Queen Speller got along into adolescent years, she stumbled over words which she knew very well, only to permit her male competitor, next in line, to profit by her mistake. Ladies, it is time to put an end to this forebearant feminine courtesy. When you know the word, *spell it out.* Your teachers and superiors, whether in business or a profession, will recognize and appreciate genuine merit. Not infrequently women of my generation were embarrassed over being elected to Phi Beta Kappa, feeling it would ruin them socially. Lucky, indeed, is that man who has a wife more intuitive, more perceptive, wiser than, and as knowledgeable as he.

The Educator's Dream

All educators would like to know how to distinguish and select young persons for their faculty who, in later years, will make an indelible impress upon their disciplines and offer a significant contribution to society. Unremitting industry, high motivation, a willingness to share, acceptance of opportunity as the greatest of all paymasters, warm appreciation of the talents of others, and a philosophic outlook revealing more than traces of interest in his fellowman: these are the special talents of those who, in life's lottery, are most likely to fulfill youthful promise. One of the primary responsibilities of educational institutions is to recognize unusual ability and reward it with the best opportunity the school can provide.

The coming of George Edgar Vincent in 1911 as Minnesota's third University President had great significance for higher education here. By the expedient of the Power of Appointment, during his all too brief six years at Minnesota, Vincent created a true University out of a collection of sleeping colleges quite happy and content in their mediocrity. Vincent obviously had that rare skill of recognizing latent talent before it had been tested and its promise known to everyone. He brought Drs. Coffey, Coffman, Ford, and Lyon, all young men, to lend wings to his own aspirations of creating a pulsating University at Minnesota. He selected leaders who reflected his own ability in finding creative associates for their respective colleges.

The Role of the Teacher in the Educative Process

Focusing the sunshine of encouragement upon the efforts of students is essentially the function of the teacher, a device which brings a bounteous return to the institution. In the leaven of an atmosphere fostering inquiry, no one should be afraid to come forward with a novel idea, no matter how strange or unfamiliar it may sound. In the crucible of experiment, amidst friendly doubting Thomases, the new idea can be given the acid test. The stages of a new idea are multiple. Many are stillborn. But every new suggestion deserves at least a trial of being blown upon in the hope there may be sparks in the ashes. The teacher who stimulates the student to apply a spur to the spring of his own mind, and removes from his path all institutional brakes and other narcotic influences, will leave his mark upon the accomplishments of his students.

There is undoubtedly emergent talent of the highest quality in members of this graduating class. How many teachers recognized such unusual promise and made telling efforts not only to encourage but also to sketch future

courses to achieve optimal opportunities for gifted students? Is that not too a function of teachers? Those of you looking forward to winning laurels in the Academic Arena will find observance of this neglected pedagogic principle a source of great strength.

Medical Research, an Exportable and International Commodity

I want to cite a type of activity which may have important connotations at the diplomacy level. When Dr. Christiaan Barnard of Cape Town came here a dozen years ago, my associates and I were keenly impressed by his abilities. It will interest you to know that with the sympathetic concurrence of Dean Blegen, many rules were fractured in getting him both a Master's and Ph.D. degree within a period of two years and nine months. Those who point to the restrictions of rules and regulations leave me colder than the principles they espouse.

Through representatives to the National Institutes of Health, a research Grant of $10,000 was obtained for Dr. Barnard to energize his work in intracardiac surgery in Cape Town. Six years after he left us in 1958, Mrs. Wangensteen and I were privileged to visit Africa. At a luncheon in Cape Town, Administrator Malan of South Africa showed me a clipping from a local newspaper which suggested I had come there primarily to proselyte for American Surgery. This intent I disavowed, but indicated I was not above attracting young graduate students from Africa to our fold because we already had four brilliant persons from that continent. Said Malan, "Doctor, if you as much as raise your finger to get Barnard a position in the United States, may I tell you, you will *never* leave this country." That Barnard fully justified the confidence which Malan held out for him in 1964, everyone now knows, for it was he who did the first successful human heart transplant in the world. It was Norman Shumway, another Minnesota protegé, who led the way with his brilliant demonstration of the feasibility of transplanting the heart.

Brains and talent are not limited to any nation or race. Over a period of long years, during which our Department of Surgery had at one time as many as twenty graduate students from foreign countries, including every continent, it was thrilling to observe the same warm response to research in many of our foreigners as in our own American students.

Need for Broader Participation by Specialists in International Diplomacy

That $10,000 for Dr. Barnard did a great deal for World Medicine and something too, I believe, for International Relations. This type of International Diplomacy, I feel must come to play a greater role in the activities of our State Department. The New York physician, Howard Rusk, Mender of the Maimed, Paul Dudley White, renowned cardiologist, Michael DeBakey, cardiovascular surgeon, and men of the stamp of the late Charles Mayo, could be very useful to a Dean Rusk in the State Department in efforts to win converts for international agreements and humanitarian values. Our negotiators over Vietnam in Paris, I believe, would be helped by the presence of medical men like Surgeon General Heaton who with associates attend the wounded and dying and whose results in the management of wounds on the field of battle have stirred the admiration of medical men everywhere. Statistics show that despite the unfavorable conditions of warfare, our

military surgeons are obtaining results in contaminated wounds in Vietnam equalling those observed in the management of clean wounds in our best Civilian Hospitals.

Our Troubled Times

Sympathy is the only universal solvent. When assailed by a critic for leniency, Lincoln replied, "Do I not destroy enemies by making them our friends?"* That concept has pertinence for us today in the resolution of domestic problems as well as at the Peace Table.

America has an important debt to pay for long years of parasitism on European culture in Medicine and Science. We have now begun to acknowledge this long-standing obligation, not alone with soul-stirring emotions of appreciation and gratitude but also, I trust, in terms of usurious dividends. Medical research, like bread, is an international commodity, and is probably the only article of commerce that is tax-free to all peoples of the world. There are no secret or confidential files in medicine. Benefactions of the latest discovery are available to everyone.

In this context, it is fitting to recall the immortal lines of Wordsworth about Milton. Paraphrased for our own times, we could say:

Lincoln, thou should be living at this hour. America has need of thee
The social structure of our beloved country is a marsh of stagnant and repellent waters.
Your compassionate wisdom would help extricate us from this dismal morass,
Compounded of neglect and lack of vision: while striving to resolve
The problems of the world, we have glossed over our own.

Need for Application of Scientific Research Methods to Social Problems

During a period of startling achievement in the natural and biological sciences, not even hoped for by our antecedents a century ago, we meet only obstructing roadblocks and disappointments in efforts to improve our social structure. We pray for peace, yet in America my generation over the past 70 years has experienced seven wars. Why so little progress in man's relation to his fellows? Why not the same concord between intent and accomplishment that attends application of scientific methods of research in the biological and natural sciences?

In 1892 many of the world's scientific leaders in medicine met in Paris to honor Pasteur for his epoch-making contributions to human welfare. Too overcome with emotion to speak, the aging Pasteur replied through the voice of his son, "Science and peace will triumph over ignorance and war; nations will unite not to destroy, but to build; the future belongs to them who do most for suffering humanity." Woodrow Wilson, Franklin Delano Roosevelt and others have echoed this theme. But we still wait, hoping and believing that the day may not be far off when men will compose their difficulties with a view to what is best for all.

We need to assess more carefully the significant difference between testimony and evidence. Traditional empiricism did precious little over the centuries to advance Medicine. Observation and experiment, with factual assessment of the data in a scientific manner, must come also to supplant our present unrealistic approaches to social problems. If only man were not an unpredictable creature of moods and prejudices! Even so it is time that we

*Carl Sandburg: Abraham Lincoln, the War Years. Vol. 3, p. 405-6.

begin to seek better orientation. The problem should ultimately yield to assessment by scientific methods. Shakespeare reminds us:

"Thoughts are but dreams till their effects be tried."

We need to energize translation of our hopeful dreams into action.

The reaction to encouragement is the same for peoples everywhere. It is their reaction to discouragement which largely distinguishes individuals. Many are dissuaded from the struggle, while the rugged few find their motivation and determination strengthened and their thinking sharpened by opposition. For all, life is an endless climb up a slope of varying pitch.

Education, the Best Means of Combatting Poverty

I am fully persuaded that if adequate facilities were provided to assure an education for all who desire it, poverty would disappear in our country. Many a rich man's only claim upon immortality is that he has educated a poor man's worthy son. This is now Uncle Sam's primary obligation. If he has enough money, man-power, and young lives to sacrifice in contesting a foreign power in a distant land, he must not overlook the education of his deserving sons and daughters. The time must come when all who seek a college education and satisfy the entrance requirements will be given the privilege. A century ago only one percent of those between 18 and 21 went to college; at the turn of the century, four percent; currently somewhat less than 50 percent. It would be in the interests of our national economy to provide free tuition for those who do not have the means. The increased enrollment would create the need for more colleges and the enlargement of existing institutions. Does not the University of Minnesota provide evidence beyond testimony that quality and quantity can cooperate at a high level of effectiveness?

Is there a Utopia?

Utopia has always been man's dream, which is a way of saying that man has an image of the way things ought to be. Some would have us believe that by upsetting the existing order one is likely to achieve the heaven of his dreams. We struggling pilgrims must endure weariness, despondency and failure, while continuing to struggle on. John Milton reminds us: "The mind is its own place, and in itself can make a heaven of hell, a hell of heaven." We all dream of what we are not but would like to be. Work is more conducive to contentment, to tranquility of mind and to sleep than are soporifics, tranquilizers, LSD, marihuana, or whiskey. Happy and fortunate is that man who throws himself with complete abandon into his work, for he will find that what began as labor has become a consuming interest. He who has learned the pleasures of work will not accept contraband. We can improve the world only by working for it, not by destroying it.

Your Alma Mater

As you search the distant horizons for the weather of the future, even though your work takes you to the other side of the world, remember that your Alma Mater, your Foster Mother, will continue to follow your course with interest and concern. Like all mothers, she is happiest when her progeny thrives. The success of her children honors a mother. Those of you who, with the years, achieve financial security beyond daily needs, like dutiful children, will want to share some of your good fortune with her.

Differences in sources of support between state-supported and voluntary institutions are lessening every day. Sharing and giving are two of the finest and most precious words in our language.

A story is told of Mrs. Dwight Morrow, our own Charles Lindbergh's mother-in-law. A friend at a Smith College reunion found her sitting alone in the chapel. Explained Mrs. Morrow: "I was just thinking how much happier I am today than I thought I would be when I sat here as a student." However much you have enjoyed your college years, I firmly believe that most, if not all of you, will be able in time to re-echo Mrs. Morrow's nice assessment of her life.

It is appropriate today to recall the words of the late poet laureate of England, John Masefield (1946) who on an occasion such as this said at the University of Sheffield: "There are few things more enduring than a University. Religions may split into sects or heresies; dynasties may perish or be supplanted, but for century after century, the University will continue and a stream of life will pass through it and the thinker and the seeker will be bound together in the undying cause of bringing thought into the world."

Your Paymasters

Early in our history, while citizens of Minnesota were struggling to bring order out of the wilderness, they planned for a great University. Mining, lumbering, milling, railroading, and agriculture have made Minnesota a productive and powerful state. When the call for creative scholarship and research is heard and answered in all the halls of our University, Minnesota's distinction as a celebrated intellectual center will match its vigor and accomplishment in service to state and nation. It is the special function of universities to strive to say the first word rather than the last; to show the way as well as to improve it.

The privileged opportunity of a university training should help you to equate values circumspectly; bend the knee *only* to goodness from which equality, justice and mercy flow. Those of you who respond to the beckoning call from Minerva to kneel before the Temple of Learning will find your lives quickened and enriched. It is the measure of the devotion that counts.

So in summing up, let me say to each of you: The vigor and enthusiasm of youth are the best of all catalysts in energizing the objectives which your University Training has brought into sharper focus. Weigh carefully your evaluation of emolument. When the joy of work becomes reward enough, we pilgrim wayfarers rediscover the most abiding satisfaction of life.

As each of you writes today a fresh line in the dictionary of your life, think also of planting a tree for Posterity in the Garden of your Dreams. It will give you enduring satisfaction, and its growth can project your image and wishes far into time and space.

On Respiration

Respiration, when frequent, indicates pain or inflammation in the parts above the diaphragm: a large respiration performed at a great interval announces delirium; but a cold respiration at nose or mouth is a very fatal symptom. Free respiration is to be looked upon as contributing much to the safety of the patient in all acute diseases, such as fevers, and those complaints which come to a crisis in forty days.*

*From Hippocrates' Book of Prognostics



Book Reviews

The good book is always a book of travel; it is about a life's journey.

—H. M. Tomlinson

ANATOMY OF THE NEWBORN, Edmund S. Crelin, Professor of Anatomy, Yale University School of Medicine, Lea & Febiger, Philadelphia, 1969.

This is a remarkably handsome Atlas consisting of 351 life-size illustrations in color. The dissection and the drawings were done by the author. In its detail, its accuracy, and its art the work is comparable to the original work of Sabotta. The index is excellent but could well be considered superfluous in view of the superb organization of the book's contents.

This work is a classic and certainly should be in the library of every pediatric surgeon.

Carl O. Rice, M.D.

PULMONARY EMPHYSEMA AND RELATED LUNG DISEASES. Author: Theodore Rodman and Francis H. Sterling, M.D. Publication Date: January 1969. Publishers: The C. V. Mosby Company. Price: $27.50.

This is an excellent book covering the diagnosis, treatment, pathology and physiology of pulmonary emphysema and related diseases. In leafing through the 449 well-written and vivid pages, one cannot escape the notion that we have come far during the last 30 years in our understanding and also in the treatment of this devastating pulmonary disease. The book is pervaded by the author's personal experience and profound knowledge. Occasionally a personal note is struck, as when the authors lament the precipitous use of oxygen in the patient's home, in the ambulance, and by eager house staff physicians, and compare this to conditions in England where the emphysema patient enters the hospital more hypercarbic than in America, albeit less hypoxic.

The chapter on complications and on abnormal physiology is splendid. Although the chapter on treatment with reference to surgery is somewhat skimpy and unsatisfactory for the chest surgeon, the interdepartmental line of communications is kept wide open by establishing the common familiar ground of physiology and pathophysiology. The medical treatment of emphysema is very adequately discussed. There is also an excellent description and tabulation on the use of oxygen, nebulizers and intermittent positive pressure breathing devices. Any physician interested in establishing a respiratory unit at his hospital would benefit from the use of this book. The pertinent physiological data are well tabulated and explained. The methods of pulmonary physiotherapy, physical medicine and rehabilitation are described in detail and are well illustrated.

This work is not only a valuable addition to every doctor's library, but it is highly recommended for continuing study and use until new developments in our understanding of emphysema and its treatment hopefully make it obsolete.

H. W. Heupel, M.D.
Minneapolis, Minnesota

HUMAN TUMOR CELL KINETICS. National Cancer Institute Monograph 30. Edited by: Seymour Perry, M.D. Publisher: Superintendent of Documents, U. S. Government Printing Office, Washington, D. C. 20402. Date: May, 1969. Price: $4.00.

A series of seminars sponsored by the National Cancer Institute of the United States Public Health Service is devoted to the subject of normal and tumor cell kinetics, especially in human neoplasia.

Fundamental data concerning cell kinetics and cell cycle characteristics of normal or neoplastic cells in man are sparse. It is evident that there is a great difference between rapidly growing and slowly growing tumors. Even within tumors of the same morphologic type, this distinction can be made. The role of cell kinetics is significant in the dosage schedule and selection of agents to be considered in cancer chemotherapy.

Since many antitumor agents affect cells in deoxyribonucleic acid synthesis or in some other phase of the mitotic cycle, tumors with a larger fraction of cells in active proliferation will be more susceptible to treatment. Tumors that are slowly growing would have fewer cells in deoxyribonucleic acid synthesis and would be less affected by therapeutic agents. Since damage to normal proliferating tissues also occurs, the ideal cancer chemotherapy should be spaced to achieve maximal antitumor effect, yet allow for repair of normal tissues.

The symposium stresses studies of cell kinetics, especially of the leukocyte, liver, intestinal epithelium, and experimental tumors, systems which allow measurements of the rapid cell changes that occur in these tissues. Considered in the various studies are problems such as generation time, size of the pool of replicating tumor cells, the death rate of tumor cells, and the replication rate of cells. The studies include the pathophysiology of psoriasis which is related to an increased rate of deoxyribonucleic acid synthesis in the abnormal cells.

There is no doubt that the pathogenesis of cell regeneration will lead to important insights about neoplastic processes, and perhaps even to improved methods of tumor control.

B. J. Kennedy, M.D.
Minneapolis, Minnesota

Convalescing . . . but still a long way to go. Anxiety can make it even longer.

Convalescence following medical or surgical procedures may be almost endless to an anxious patient. And, indeed, anxiety with some patients actually retards progress—for example, by inducing insomnia and reducing cooperation.

As physicians have found during nearly 15 years of widespread use, Equanil may be a beneficial part of aftercare. It helps relieve anxiety and tension, thus often aiding your primary therapy.

Indications: For use in management of anxiety and tension occurring alone or as accompanying symptom complex to medical and surgical disorders and procedures. Though not a hypnotic, fosters normal sleep through antianxiety and related muscle-relaxant properties.

Contraindications: History of sensitivity to meprobamate.

Important Precautions: Carefully supervise dose and amounts prescribed, especially for patients prone to overdose themselves. Excessive prolonged use has been reported to result in dependence or habituation in susceptible persons, as alcoholics, ex-addicts, and other severe psychoneurotics. After prolonged excessive dosage, reduce dosage gradually to avoid possibly severe withdrawal reactions. Abrupt discontinuance of excessive doses has sometimes resulted in epileptiform seizures.

Warn patients of possible reduced alcohol tolerance, with resultant slowing of reaction time and impairment of judgment and coordination.

Reduce dose if drowsiness, ataxia or visual disturbance occurs; if persistent, patients should not operate vehicles or dangerous machinery.

Side Effects include drowsiness, usually transient; if persistent and associated with ataxia, usually responds to dose reduction; occasionally concomitant CNS stimulants (amphetamine, mephentermine sulfate) are desirable. Allergic or idiosyncratic reactions are rare, but such reactions, sometimes severe, can develop in patients receiving only 1 to 4 doses who have had no previous contact with meprobamate. Previous history of allergy may or may not be related to incidence of reactions. Mild reactions are characterized by itchy urticarial or erythematous maculopapular rash, generalized or confined to groin. Acute nonthrombocytopenic purpura with cutaneous petechiae, ecchymoses, peripheral edema and fever have been reported. One fatal case of bullous dermatitis following intermittent use of meprobamate with prednisolone has been reported. If allergic reaction occurs, meprobamate should be stopped and not reinstituted. Severe reactions, observed very rarely, include angioneurotic edema, bronchial spasms, fever, fainting spells, hypotensive crises (1 fatal case), anaphylaxis, stomatitis and proctitis (1 case) and hyperthermia. Treat symptomatically as with epinephrine, antihistamine and possibly hydrocortisone. Aplastic anemia (1 fatal case), thrombocytopenic purpura, agranulocytosis and hemolytic anemia have occurred rarely, almost always in presence of known toxic agents. A few cases of leukopenia, usually transient, have been reported on continuous administration.

Meprobamate may sometimes precipitate grand mal attacks in patients susceptible to both grand and petit mal. Extremely large doses can produce rhythmic fast activity in the cortical pattern. Impairment of accommodation and visual acuity has been reported rarely. After excessive dosage for weeks or months, withdraw gradually (1 or 2 weeks) to avoid recurrence of pretreatment symptoms (insomnia, severe anxiety, anorexia). Abrupt discontinuance of excessive doses has sometimes resulted in vomiting, ataxia, tremors, muscle twitching and epileptiform seizures. Prescribe very cautiously and in small amounts for patients with suicidal tendencies. Suicidal attempts have resulted in coma, shock, vasomotor and respiratory collapse and anuria. Excessive doses have resulted in prompt sleep; reduction of blood pressure, pulse and respiratory rates to basal levels; and occasionally hyperventilation. Treat with immediate gastric lavage and appropriate symptomatic therapy. (CNS stimulants and pressor amines as indicated.) Doses above 2400 mg./day are not recommended.

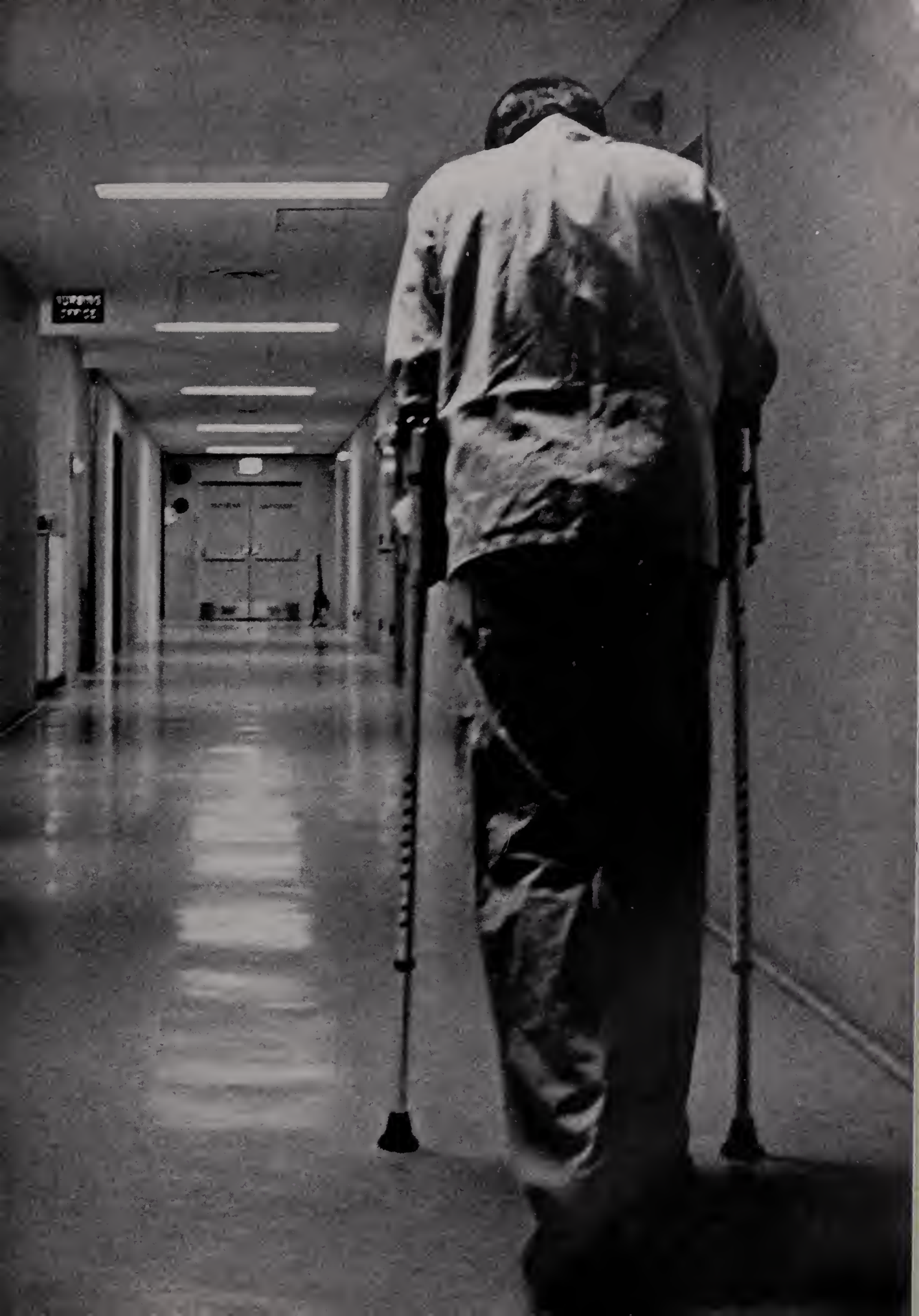
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Continued from page 68.

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WANTED: General Practitioner or Internist, to join four man group in St. Paul. Partnership possible in one year. Dr. V. L. Sommerdorf, 1239 Payne Avenue, St. Paul, Minnesota 55101.

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OPPORTUNITY for career in occupational medicine with large corporation. Multiple locations. Salary plus fringes. Immediate openings in three locations. Give résumé. Write MINNESOTA MEDICINE—432, 375 Jackson, St. Paul 55101.

NEW EXPANDING OPPORTUNITIES for family physicians and physicians specializing in pediatrics, general surgery, internal medicine, urology, radiology, anaesthesiology; in medically-awakening community. Contemporary, automated, 105-bed, new hospital to be completed in the fall of 1970. Present hospital to be converted into long-term unit. Patient service area 50,000 people. Medical staff leading and supporting recruitment efforts. Excellent community location, forty miles equidistant to Milwaukee or Madison. Complete educational, cultural and recreational facilities. Possibility of new medical office building adjacent to new hospital. Immediate satisfaction in practice, income and family living. Special assistance if needed. Write or call Leo C. Bargielski, Administrator, Watertown Memorial Hospital, 1301 E. Main Street, Watertown, Wisconsin, 53094; telephone 414-261-4210 for more information.

GP AND OB GYN wanted to join two GPs, surgeon, and internist in suburban group. Excellent nearby hospital. Salary first year, then partnership. Write MINNESOTA MEDICINE-436, 375 Jackson, St. Paul 55101.

POSITION OPEN—Assistant Medical Director, under age 40, 37½ hour work week, liberal vacation and other fringe benefits including pension plan. Contact C. A. Nordin, M.D., Equitable of Iowa, Box 1635, Des Moines, Iowa, 50306. Phone 515-284-6755.

GP: To join young two man group in family practice. Immediate work load. $25,000 salary first year with opportunity for early full partnership. Well-equipped clinic established in 1956. New building built 1967. Situated in fast-growing suburb of Des Moines. Contact Don C. Green, M.D., 6762 Douglas, Des Moines, Iowa 50322.

WANTED: General practitioners and interested specialists to meet the medical needs of a fast-growing suburban community of St. Paul. Local physicians cannot handle the requests for medical attention and will refer patients to new physicians practicing in the area. Have information on several office sites (some equipped) for sale or lease to assist in getting established. An all-modern, fully accredited hospital available. Open staff. A hospital consulting firm studying present and future needs for both hospital and professional facilities. An excellent opportunity that has to be very attractive financially. Phone 227-7001 and ask for the Administrator.

LARGE PEDS PRACTICE—Immediately available practice of William R. Heilig, M.D., deceased—$60,000.00 gross last year—900 square feet—5 examining rooms—laboratory—private office—reception and administrative area—all fully equipped at Midway Center at 1562 University Avenue, between Minneapolis and St. Paul. First floor space with adjacent free parking area—rent $378.00 per month—flexible terms from estate. Mrs. William R. Heilig, 5501 Glengarry Parkway, Edina, Minnesota 55436, Telephone: (612) 929-6485.

GENERALIST — INTERNIST — OPHTHALMOLOGIST NEEDED IN FAIRMONT, MINNESOTA. Will begin construction of a new 115 bed hospital and a large medical clinic next spring. Lovely community of 13,000 population centered around a chain of lakes in Southern Minnesota. Excellent public schools with a new junior college scheduled to open in 1973. Two doctors' offices presently have space for another man. Call or write Robert Zemke, Generalist, Neil Nickerson, Internist or Cale Neal, Hospital Administrator.

OPERATING DOCTORS CLINIC FOR SALE — Sealed bids will be received on the Two Doctor Clinic in Sandstone. 44 x 44 ft. brick veneer building only five years old, full basement, 105 x 60 lot, Sears Foundation Plan, adjacent to busy County Hospital.

Bids to include cashiers check or acceptable bid bond for 5% of bid. Bids to be opened on Jan. 12, 1970, 7:30 P.M. Directors reserve the right to accept or reject any or all bids. Notice of awards within 30 days. Sandstone Development Corporation, Sandstone, Minnesota 55072.

Annual Meeting

The thirty-third annual meeting of The New Orleans Graduate Medical Assembly will be held March 2, 3, 4, 5, 1970, at The Roosevelt Hotel. Nineteen outstanding guest speakers will participate and their presentations will be of interest to both specialists and general practitioners. For further information, contact Secretary, Room 1538, 1430 Tulane Avenue, New Orleans, Louisiana 70112.

Minnesota Medicine at a Glance

Toxoplasma Gondii Infections—*Theologides* Page 21

Treatment of choice is a combination of sulfonamides and pyrimethamine.

Toxoplasmosis is a rarely recognized systemic disease affecting many organs of the body. It exists as a congenital condition or postnatal infection; it may be of the glandular type, localized type in one organ, or cerebral toxoplasmosis, myocarditis, pulmonary toxoplasmosis, hepatitis and ocular toxoplasmosis.

Cryosurgery in Otolaryngology—*DeSanto* Page 29

The advent of new cryosurgical apparatus, using either liquid nitrogen or liquid freon, has opened this new field to the otolaryngologist. The author reviews in this issue the present-day experience with this new method and speculates on its further application. With the use of narrow probes, freezing and tissue necrosis can be effected; and the extent of the necrosis and of the following tissue sloughing can be exactly predicted. A particularly safe feature is the resistance of large vessels to freezing and necrosis, thus avoiding the danger of major hemorrhage inherent in other surgical methods. Cryosurgery is now being used for the treatment of painful disorders in the head and neck area, in the treatment of Meniere's disease, epistaxis and nasal polyps, and for the destruction of the pituitary gland. Tonsillectomies may be performed by this method in patients where bleeding is a problem; it has a place in the eradication as well as in the palliation of certain head and neck tumors. The authors advocate further standardization of the treatment in order to make its effects more predictable. A combination of cryosurgery, chemotherapy and irradiation for the treatment of malignant tumors is envisioned. It may become a valuable tool in the early eradication of cancer of the vocal cords.

Pre-eruptive Varicella Encephalitis Presenting as Status Epilepticus—*Resnick* Page 65

Although encephalitis is a relatively rare complication of varicella, it is still the most common and serious of the neurologic sequelae. The author discusses an unusual case of pre-eruptive varicella encephalitis which may be recognized by an alert careful inquiry into a child's history of infectious exposure. An excellent review of the literature regarding varicella encephalitis is also included.

Coincidence?

Is it entirely a coincidence that of all cultures, that of the present-day West is the most time-conscious? That it has spent more of its energies in studying time, measuring time, cutting time up into ever-tinier segments with ever-greater accuracy?

Is it entirely a coincidence that the most materialistic subdivision of our most materialistic culture, the twentieth-century American, is never seen anywhere without his wristwatch? At no time, apparently, dare he be unaware of the sweep of the second hand and of the ticks that mark off the inexorable running out of the sands of his life.*

*Isaac Asimov: Of Time and Space and Other Things, 1965.

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Contraindications: Concurrently with MAO inhibitors, in patients hypersensitive to this drug; in emotionally unstable patients susceptible to drug abuse.

Warning: Although generally safer than the amphetamines, use with great caution in patients with severe hypertension or severe cardiovascular disease. Do not use during first trimester of pregnancy unless potential benefits outweigh potential risks.

Adverse Reactions: Rarely severe enough to require discontinuation of therapy, unpleasant symptoms with diethylpropion hydrochloride have been reported to occur in relatively low incidence. As is characteristic of sympathomimetic agents, it may occasionally cause CNS effects such as insomnia, nervousness, dizziness, anxiety, and jitteriness. In contrast, CNS depression has been reported. In a few epileptics an increase in convulsive episodes has been reported. Sympathomimetic cardiovascular effects reported include ones such as tachycardia, precordial pain, arrhythmia, palpitation, and increased blood pressure. One published report described T-wave changes in the ECG of a healthy young male after ingestion of diethylpropion hydrochloride; this was an isolated experience, which has not been reported by others. Allergic phenomena reported include such conditions as rash, urticaria, ecchymosis, and erythema. Gastrointestinal effects such as diarrhea, constipation, nausea, vomiting, and abdominal discomfort have been reported. Specific reports on the hematopoietic system include two each of bone marrow depression, agranulocytosis, and leukopenia. A variety of miscellaneous adverse reactions have been reported by physicians. These include complaints such as dry mouth, headache, dyspnea, menstrual upset, hair loss, muscle pain, decreased libido, dysuria, and polyuria.

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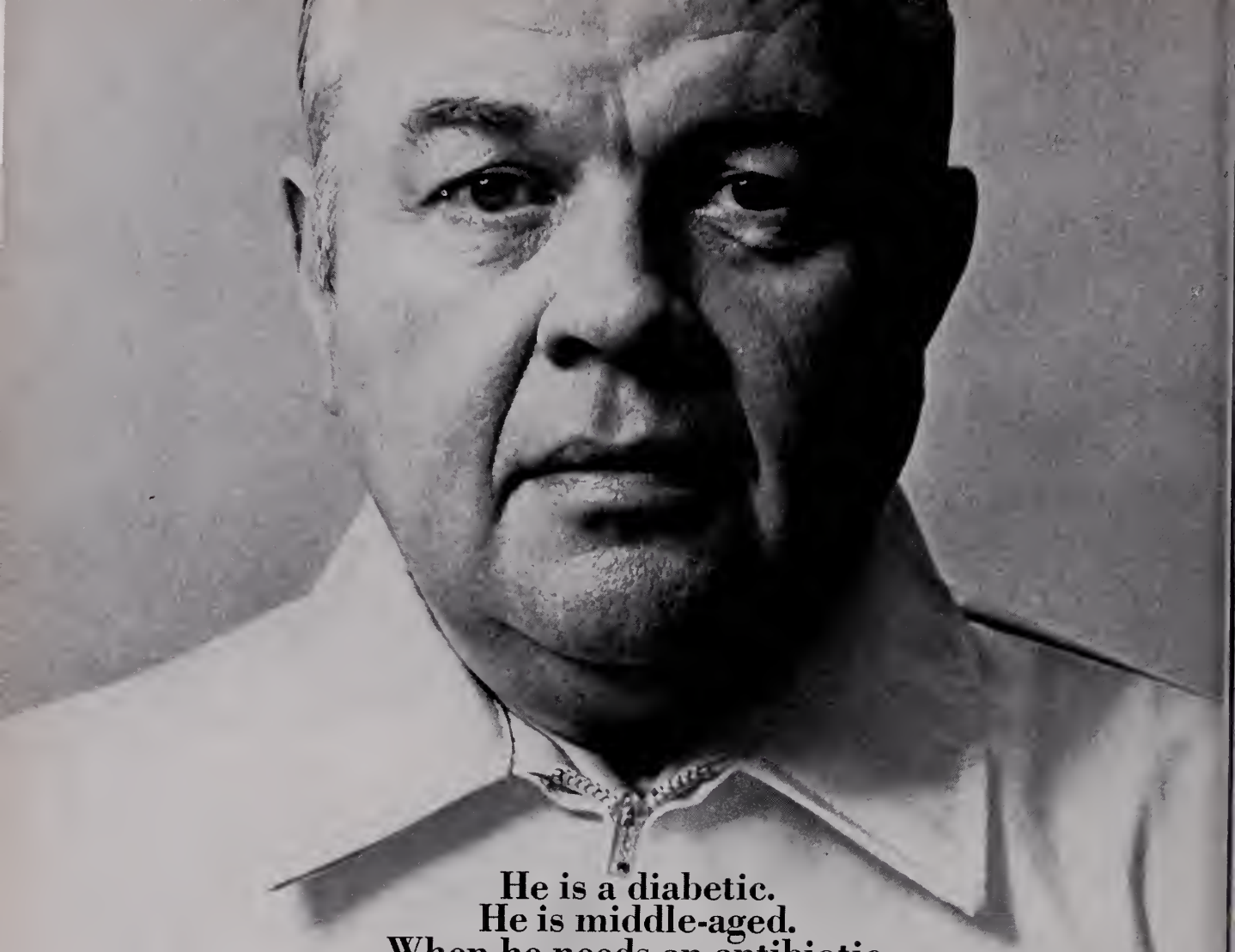
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(In vivo measurement of Lutrexin on contracting uterine muscle of the guinea pig.)

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Contraindication: History of hypersensitivity to demethylchlortetracycline or nystatin.

Warning: In renal impairment, usual doses may lead to excessive accumulation and liver toxicity. Under such conditions, lower than usual doses are indicated, and, if therapy is prolonged, serum level determinations may be advisable. A photodynamic reaction to natural or artificial sunlight has been observed. Small amounts of drug and short exposure may produce an exaggerated sunburn reaction which may range from erythema to severe skin manifestations. In a smaller proportion, photoallergic reactions have been reported. Patients should avoid direct exposure to sunlight and discontinue drug at the first evidence of skin discomfort. Necessary subsequent courses of treatment with tetracyclines should be carefully observed.

Precautions: Overgrowth of nonsusceptible organisms may occur. Co stant observation is essential. If new infections appear, appropria measures should be taken. In infants, increased intracranial presst with bulging fontanels has been observed. All signs and symptoms ha disappeared rapidly upon cessation of treatment.

Side Effects: Gastrointestinal system—anorexia, nausea, vomiting, di rhea, stomatitis, glossitis, enterocolitis, pruritus ani. Skin—maculop ular and erythematous rashes; a rare case of exfoliative dermatitis h been reported. Photosensitivity; onycholysis and discoloration of t nails (rare). Kidney—rise in BUN, apparently dose related. Transi increase in urinary output, sometimes accompanied by thirst (rar Hypersensitivity reactions—urticaria, angioneurotic edema, anaphyla Teeth—dental staining (yellow-brown) in children of mothers given t drug during the latter half of pregnancy, and in children given the dr during the neonatal period, infancy and early childhood. Enamel hy plasia has been seen in a few children. If adverse reaction or idios crasy occurs, discontinue medication and institute appropriate thera Demethylchlortetracycline may form a stable calcium complex in a bone-forming tissue with no serious harmful effects reported thus in humans.

Average Adult Daily Dosage: 150 mg q.i.d. or 300 mg b.i.d. Should given 1 hour before or 2 hours after meals, since absorption is impai by the concomitant administration of high calcium content drugs, fo and some dairy products. Treatment of streptococcal infections sho continue for 10 days, even though symptoms have subsided.

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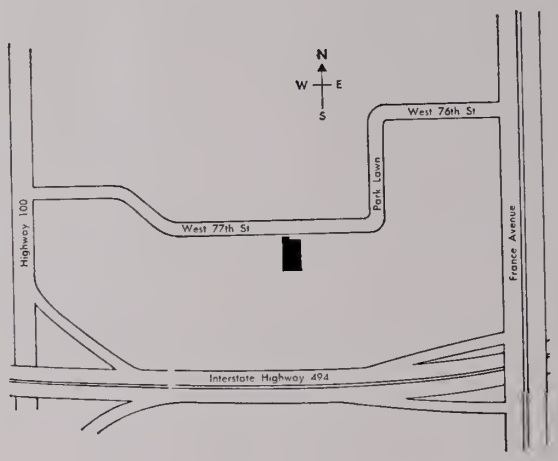
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President's Letter

As discussed in the President's letter of January,* the Committee on Standards of Medical Care of the Minnesota State Medical Association is in the process of establishing a statewide central organization to provide utilization review services to physicians and hospitals and compile and analyze data relative to patient care.

The Medicare law requires that utilization review be done at the community level. The State Department of Health is charged by law with the responsibility of certifying hospitals, extended care facilities and nursing homes for participation in the Medicare program and has a statutory obligation under Title XVIII to do a continuing assessment of effectiveness of utilization review. Their findings must be reported to H.E.W. The carriers are also required to establish guidelines for utilization review and they have been doing limited audits and are prepared to expand their activities in this field. It was, therefore, imperative that if the medical profession of Minnesota was to assume responsibility and provide leadership in the field of utilization review, it had to act promptly. The Committee on Standards of Medical Care has now been able to establish a facility within the framework of the Minnesota State Medical Association with space in the Association offices to do utilization review on a statewide scale.

The staff of this organization will include a full-time physician as Medical Director, who has already been obtained, a biostatistician and a secretary. A team of technical persons will be hired to do audit screening, and the actual evaluation of this data will be performed by physicians selected on the basis of demonstrated competence and leadership in their respective specialties and communities. Privacy and confidentiality of information will be ensured at all times by eliminating names of patients, attending physicians and hospitals and using code numbers for their identity.

The facility will be under the guidance of the Committee on Standards of Medical Care and ex-officio members will be added to the Committee to help provide expertise knowledge from the following organizations: The Minnesota Blue Cross, Minnesota Blue Shield, Minnesota State Board of Health, Minnesota Department of Public Welfare, Northlands Regional Medical Program, Minnesota Hospital Association and the Minnesota Association of Record Librarians.

The Utilization Review facility will likely start cautiously but with vigor. It will probably first do feasibility studies but eventually establish profiles and patterns of disease for comparison and statistical evaluation. This data will be used for educational purposes to aid the physician in determining his needs as well as the needs of the patient, pointing the way to better health at a reasonable cost and thus providing more efficient delivery of health care services.

I ask all physicians in Minnesota to support this program to the fullest extent. It is by establishing such a facility aimed at raising medical standards and assuring reasonable costs of medical care that the profession can regain some of the respect and confidence of the general public that has been eroded away in recent years.

I wish to extend congratulations to the authors of the several outstanding papers presented in this Special Issue of MINNESOTA MEDICINE. The papers by this group of authors from the Metropolitan Medical Center in Minneapolis is a fine example of what physicians in our midst can do. I salute you.

Delmar R. Gillespie

Delmar R. Gillespie, M.D.
President
Minnesota State Medical Association

*See page 7.

STATE MEDICAL ASSOCIATION

minnesota medicine

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Cecal Carcinoma Causing Acute Appendicitis

Case in a Young Woman

RICHARD L. REECE, M.D.
Minneapolis, Minnesota

For a 25-year-old woman to have acute appendicitis is common. But for so young a woman to have acute appendicitis caused by a cecal carcinoma blocking the appendiceal lumen must be exceedingly rare. At least I have been unable to find a similar case in this young a person. I should like to relate her story.

Case Report

A 25-year-old single white woman awoke at 2 A.M. on February 2, 1966, because of vague abdominal distress. Within three hours, pain localized to the right lower abdominal quadrant. By 11 A.M. she was doubled over with pain and vomiting.

When she arrived at the hospital, she had tenderness in the right lower abdomen, a fever of 101, and a white count of 21,500 with 88 percent polymorphonuclear leukocytes. A colon x-ray was interpreted as normal. Later that same afternoon, a surgeon resected an acutely inflamed appendix coated with serosal exudate. Located retrocecally, the appendix was buried in the posterior peritoneal wall.

Tumor at Appendiceal Orifice

As he removed the appendix, the surgeon palpated through the cecal base a collar of firm tissue surrounding the orifice of the appendix. He removed a wedge of cecum containing most of this mass.

The pathologist described a 2 by 1.5-cm. cauliflower mass encroaching on and plugging the appendiceal lumen (Figure 1). Microscopically, the sessile mass consisted of hyperplastic, well differentiated, colonic glands arranged as flattened fronds (Figure 2). After consulting with other pathologists, both at his own and at other institutions, he diagnosed the lesion as "probable benign polyposis, causing acute suppurative appendicitis." He suggested the possibility of diffuse colonic polyposis elsewhere in the bowel, but these lesions were not seen on further colon x-rays.

Recurrent Tumor at Cecum

When the patient returned to the hospital two years later on February 29, 1968, she had a palpable mass in the right lower abdomen. On barium enema this appeared as a 7-cm. lesion at the ileocecal valve. The surgeon removed the right colon. At the base of the cecum arose a fungating tumor that penetrated the wall and spread to nearby nodes. During surgery, he also palpated a 3-cm. metastatic mass in the right liver lobe.

The patient returned to the hospital in June of 1968 because of an incomplete abortion. No progression of tumor was observed. In October of 1968 she returned

again, this time with right upper quadrant pain, tenderness, and a high sedimentation rate. The surgeon resected a gallbladder filled with stones and again palpated the liver, where he observed a mass in the right lobe. A biopsied lymph node was negative.

Metastases

After her discharge the patient began to complain of back pain and was readmitted in July of 1969. She had lost 21 pounds and complained of pain at the base of her cervical spine and of shortness of breath. An x-ray disclosed a fractured sixth cervical vertebra. She received x-ray treatment to this vertebra, and her pain regressed. A chemistry graph showed a high alkaline phosphatase, lactic dehydrogenase, and serum glutamic oxaloacetic transaminase (Figure 3) which was attributed to liver metastasis. A chest x-ray showed metastatic lesions in both lungs.

She then steadily lost weight and became weak with increasing dyspnea. She returned to the hospital on September 12 for terminal care. Her white count was 20,000, and she showed extreme elevations of alkaline phosphatase, lactic dehydrogenase, and serum glutamic oxaloacetic transaminase (Figure 3). She continued to slip with increasing weakness and severe pain. She died on the morning of October 6, 1969.

Autopsy

At autopsy, I observed tumor deposits in liver, lymph nodes, lungs, adrenals, cervical spine, retroperitoneal space, ovaries, and uterus. In the 2300-gram liver, large tumor nodules replaced about 50 percent of the parenchyma; in the lungs, tumor masses plugged lymphatics, beading pleural surfaces and giving a leathery consistency to the lungs.

Discussion

According to the late Harvey Cushing, every patient provides two questions: ". . . firstly what can be learnt from him and secondly what can be done for him."[1] A case report ought to answer the same questions, so that readers may profit when faced with a similar patient.

What could have been done for this patient? With hindsight, the answer is easy. When the appendix and segment of cecum were resected in 1966, the right colon should also have been removed. But a group of pathologists called the initial cecal lesion "probably benign polyposis." Now, of course, it is apparent that the lesion must have been an early carcinoma.

What can be learned from this case? 1, that surgeons should palpate the base of the cecum, even in young patients, to feel if a tumor blocks the lumen. 2, that the first chance to remove a cecal carcinoma is the best, and that a right hemicolectomy is the best procedure.

This case also affords the opportunity to cull similar cases from past journals. For a cecal carcinoma to block the appendiceal lumen and to produce appendicitis has been reported—but rarely. In a remarkable review of 71,000 appendices removed in operations with a preoperative diagnosis of acute appendicitis, Collins did not report a single similar case.[2] He recorded 74 primary carcinomas of the cecum, but none obstructed the lumen to cause appendicitis. And, in one table, he listed 71 "Obstructive Lesions of the Left Colon, Appendicitis is secondary."

On the other hand, Hossain, writing in the British Medical Journal in 1962, reported seven patients with unrecognized carcinoma of the cecum presenting as acute appendicitis or ap-

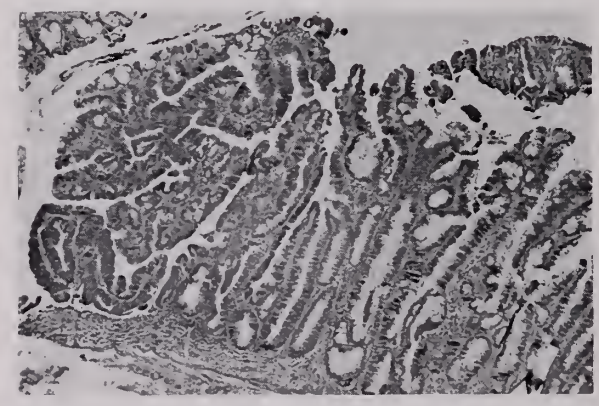


Fig. 1—Longitudinal section from appendiceal orifice showing fronds of hyperplastic colonic epithelium nearly obstructing lumen.

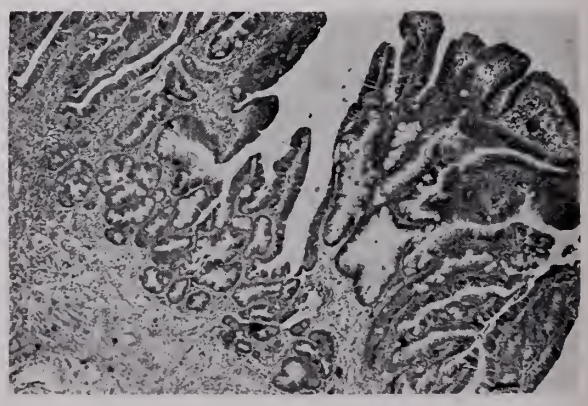
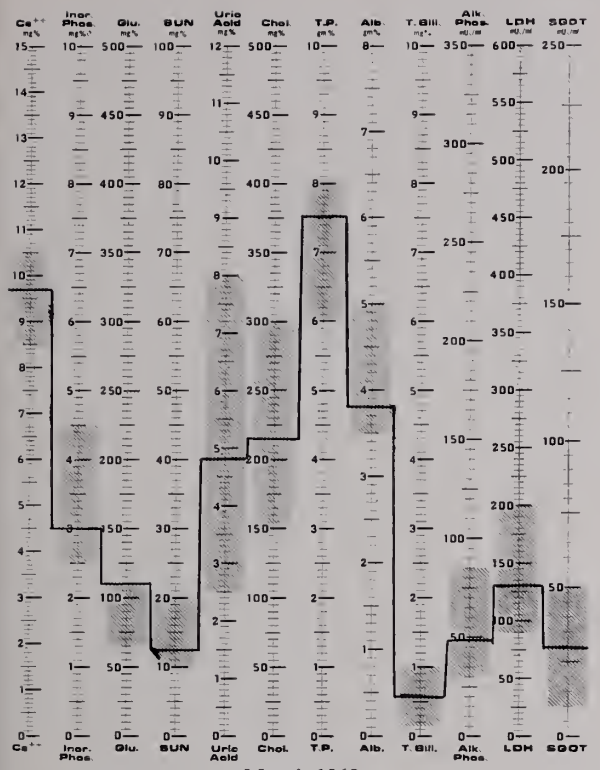
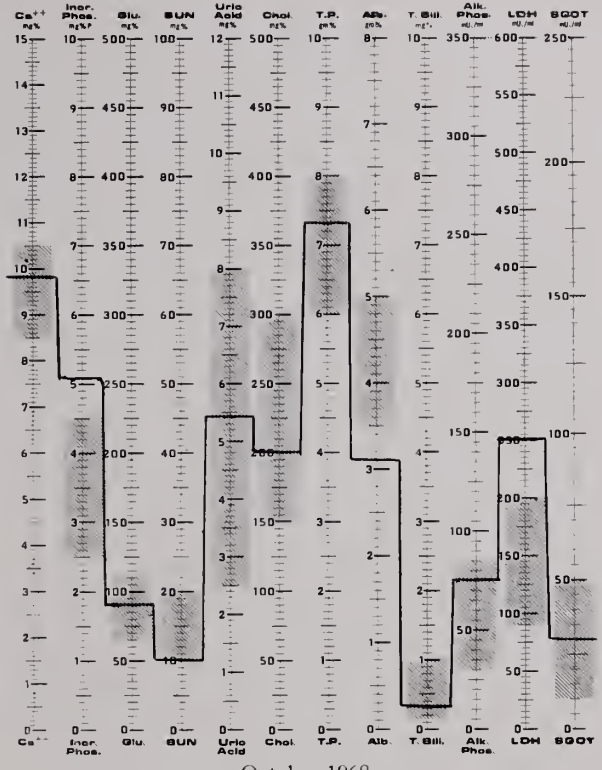


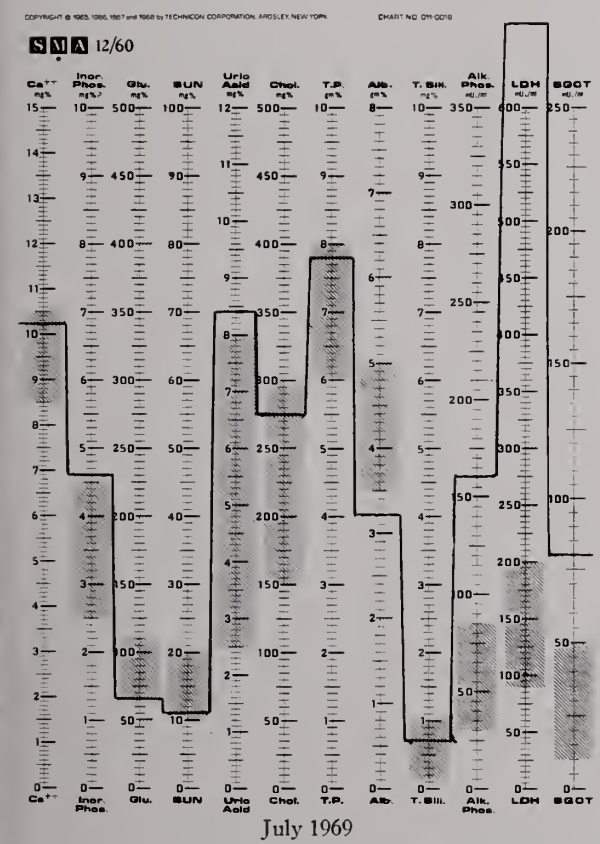
Fig. 2.—Higher magnification of colon lesion demonstrating benign, well-differentiated, polypoid appearance of tumor.



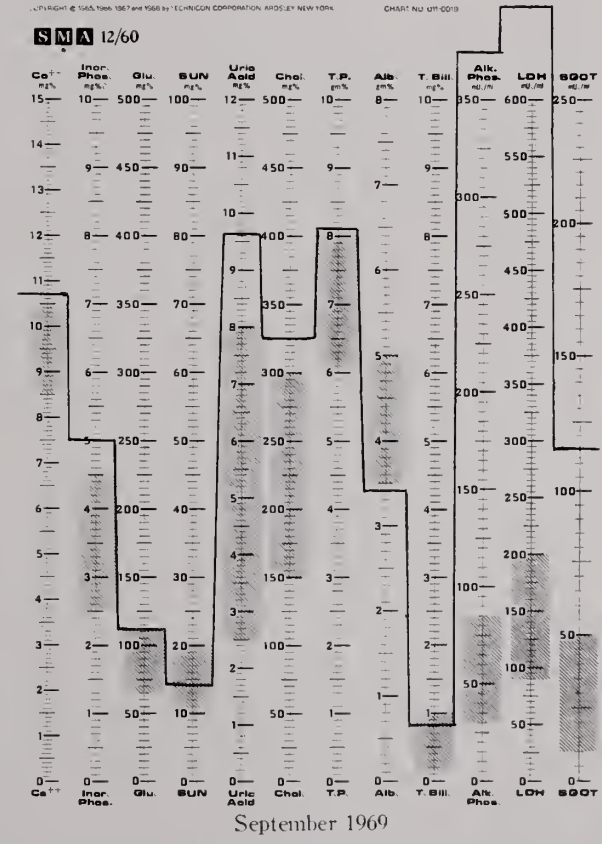
March 1968



October 1968



July 1969



September 1969

Fig. 3—Evolution of a chemical metastatic pattern. In March, 1968, patient already had 3-cm metastatic nodule in liver, but no chemical sign of spread. First chemical sign of metastases did not become apparent until October 1968—seven months later—when LDH started to rise along with phosphorus. By July 1969, tumor had extended into lungs, bone and liver, and all enzymes and uric acid were on rise. In September, 1969, just before death, all tests were still going up, and hypercalcemia had made its appearance.

pendiceal abscess.[3] He also gathered 79 cases of the "dual condition" from the literature.[1] In only one of his patients did the tumor plug the lumen; in the others it invaded the base of the appendix or blocked appendiceal lymphatics. A year later, in a letter to the British Medical Journal, he and a colleague added two cases in which the tumor actually obstructed the lumen.[4] The youngest patient reported in Hossain's or other series was 43 years old.

Since 1963, I have been unable to locate in the *Index Medicus* further cases of appendiceal lumen obstruction by a primary cecal carcinoma. Latchis and Canter wrote of a patient where metastatic breast tumor caused acute appendicitis,[5] and Schwartz and Delman noted the same pathological event with metastatic colon cancer.[6] But these were metastatic tumors, not primary cecal neoplasms.

There is one final point to be learned from this patient—how a metastatic lesion manifests itself chemically. This young lady had five survey chemistry graphs—the first in March, 1968, when the surgeon resected her cecal carcinoma and palpated a 3-cm. mass in the right lobe of the liver; the second in June, 1968, when the patient had an incomplete abortion but showed no further clinical progression of her tumor; the third in October, 1968, when her gallbladder was removed and the liver mass had "not appreciably changed in size;" the fourth in July, 1969, when the tumor had spread to a cervical vertebra and the lungs; and the fifth in September, 1969, when the tumor had metastasized further and she was on her deathbed (Figure 3).

Summary

I have reviewed the story of a 25-year-old white woman who had an early cecal carcinoma that blocked the appendiceal lumen, causing acute suppurative appendicitis. Although the primary tumor was removed two years later, the tumor metastasized to other organs, resulting in death 45 months after appendectomy.

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It's the Law

$47,500 Award Affirmed in Foot Drop Case

The patient involved suffered chronic localized osteomyelitis of the right hip since childhood. An operation was performed to correct an abscess. During this operation, part of the femur was removed. The operation was performed near the sciatic nerve. Postoperatively the patient developed a foot drop which persisted despite treatment. Evidence presented to the jury established that there was a minimum of five possible causes of foot drop. The resolution of those conflicts in expert testimony was left for the jury. The jury awarded a $47,500 malpractice award to the patient.

Jackson, P2d (Oklahoma—July 8, 1969).

To me the charm of an encyclopedia is that it knows—and I needn't.—Francis Yeats-Brown

Squamous Cell Carcinoma

Anterior Floor of the Mouth

HARRISON H. FARLEY, M.D.
Minneapolis, Minnesota

SQUAMOUS CELL CARCINOMA arising in the floor of the mouth and anterior two thirds of the tongue is best treated from a curative standpoint by surgical removal with an incontinuity dissection of the lymph nodes on the appropriate side or sides. Where the lesion is lateral this usually involves removing the adjacent mandible, which gives a disfiguring but functionally satisfactory result. Kremen,[1] in 1951, described a technique whereby the mandible was divided anteriorly and then reconstructed after the primary and lymph nodes were removed. If the tumor is close to the mandible he recommended the periosteum be peeled away in the resection, thus providing an excellent cosmetic result. However, if a considerable amount of tongue has to be removed in order to encompass the primary lesion, the end result, although cosmetically pleasing, may be functionally poor because of tongue binding in the new floor of the oral cavity.

Gowen[2] modified the technique to overcome this tightness by bringing a full thickness skin flap up under the mandible to restore a mobile floor of pliable tissue between the tongue and the reconstituted mandible.

In the case presented, the carcinoma in the floor of the mouth was directly anterior. If the mandible were to be removed in this instance the resulting deformity would have been unsatisfactory both from a cosmetic and a functional standpoint. If, on the other hand, the mandible had been divided and reconstructed with the remaining tongue used to close the gap there would have been an unacceptable tightness produced in the floor of the mouth. For these reasons a resection fashioned after the technique described by Kremen was used and reconstruction accomplished in a manner only slightly different from that described by Gowan.

Case History

A 64-year-old bartender saw his local physician in February of 1968 complaining of a sore throat of a few days' duration. Inspection revealed a large lesion in the anterior floor of the mouth measuring 3.5 × 2.5 cm. in

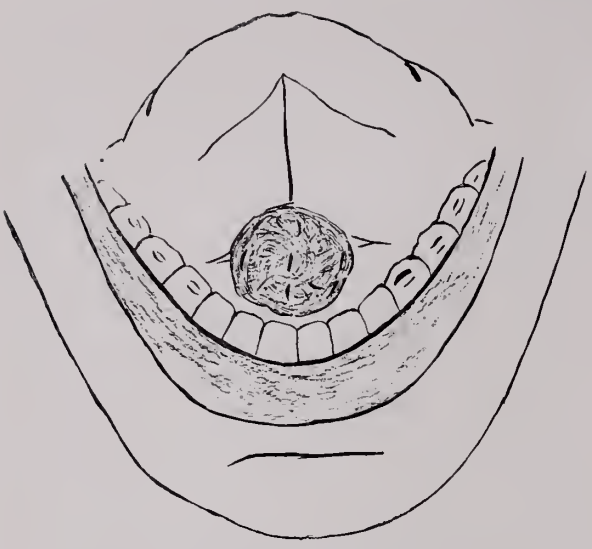


Fig. A—Lesion in the anterior floor of the mouth.

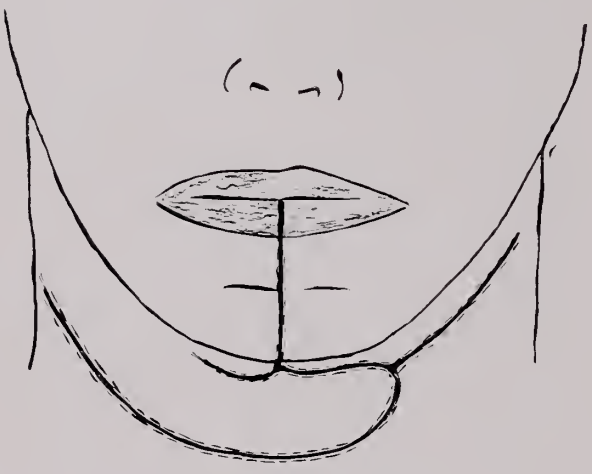


Fig. B—Outline of skin incision.

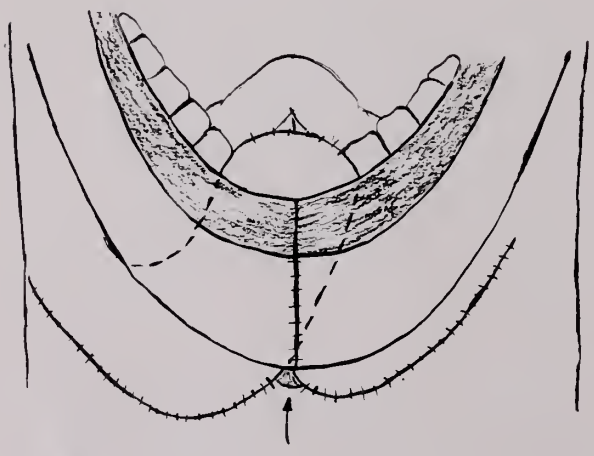


Fig. C—Rotated submandibular pedicle graft.

the region of the frenulum, extending equally to each side of the midline and invading the root of the tongue (Figure A). The lesion was movable and there were no nodes palpable on either side of the neck. X-rays revealed no evidence of mandibular destruction and there was approximately 1 cm. of margin between the tumor and the bone.

On March 1, 1968, a bilateral suprahyoid neck dissection was performed with an en-bloc resection of the tumor after dividing the mandible at the symphysis (Figure B). The periosteum was stripped away with the resection. After removal of the specimen a full-thickness pedicle graft from the neck which had been outlined in the flap dissection was rotated up to the free edge of the remaining tongue, thus forming a new but mobile anterior floor of the mouth. The mandibular continuity was restored over the flap with wire sutures. The skin flaps were undermined and shifted so that only a small oral cutaneous fistula remained and no skin graft was required (Figure C). A tracheostomy was performed at the end of the procedure.

The patient's postoperative course was remarkable in that there was only a small amount of salivary drainage from the fistulous tract. The hair-containing epidermis in the oral cavity sloughed, but the surface re-epithelialized from the adjacent mucosa. On April 24, 1968, the fistulous tract was closed at surgery (Figure D).

Discussion

The extent of the node removal was limited in this case to a bilateral suprahyoid dissection for several reasons. First, there were no palpable nodes on either side and second, in order to be complete a bilateral radical neck dissection would have had to be performed because the lesion was midline in position. The added risk of extensive flap dissection and reconstruction over a bilateral radical neck dissection seemed to outweigh the increase in cure rate that would occur because of removal of clinically negative but microscopically positive lymph nodes. Unfortunately, spread of tumor did occur on the right side. A recurrence in the right side of the neck was detected on follow-up office examination in November 1968. Five thousand r of irradiation were delivered to the neck with evidence of reduction in size of the metastasis, followed by a full neck dissection on that side on January 14, 1969. On microscopic examination no visible tumor could be detected in the resected specimen. When last seen in March of 1969, the patient was doing well with no evidence of recurrence.

At this point we certainly can not speak of curing the patient because of the short follow-up. Also there was a superficial slough of the



Fig. D—Closure of fistula.



Fig. E—Completed result.

epidermis on the portion of the flap in the mouth, which eventually resurfaced with mucous membrane. The patient did get an excellent cosmetic[e] and functional result. There is less tongue binding now than when he presented himself for treatment originally and his dentist has fashioned a lower denture for him.

Statistics show that over the past 15 years there has been no significant change in the incidence of oral cancer (Figure 1). This is not surprising, for the two commonly associated factors (smoking and poor dental hygiene) are still prevalent. Hopefully in the future a more satisfactory treatment will be forthcoming than is available with present-day surgical and radiotherapeutic techniques. In the meantime, greater attention to cosmetic and functional aspects of the surgical approach will allow the patients to return to their homes and be more acceptable to their families and friends. Perhaps this will also encourage other patients to come for treatment when their lesions are small, thereby increasing the chance for cure.[4]

Addendum

Multiple pulmonary metastases were seen on chest x-ray when patient was admitted for cholecystitis in January, 1970.

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Pulheems

(A system of medical classification)

P—physical capacity
U—upper limbs
L—lower limbs
H—hearing (acuity)
EE—eyesight (visual acuity)
M—mental capacity
S—stability (emotional)

Religion of a Doctor

Sir Thomas Browne

"For my Religion, though there be several Circumstances that might perswade the world I have none at all, (as the general scandal of my Profession, the natural course of my Studies), yet in despight hereof, I dare without usurpation assume the honorable Stile of a Christian."

Religio Medici and Sir Thomas Browne are synonymous. If the title sounds paradoxical, that is because religion and medicine appear to be dichotomous. However, the more naive and less uncompromising mind is assailed by no such apparent contradiction; if science can't square with religion, then compartmentalize: man's ever-reliable and convenient recourse when he can't integrate conflicting ideas.

Such a mind had Sir Thomas Browne (1605-1682) who studied on the Continent, took his degree in Protestant Holland, practiced medicine in Norwich, England, and wrote Religio Medici before he was 30 years old. Committed to the Church of England and its doctrine Browne was, nevertheless, a latitudinarian,* for, by virtue of identifying himself as a citizen of the world, he was tolerant of divergent views in religion: a heterodox attitude that hinted too much of heresy in a narrow-minded age still adhering to religious medievalism and resisting advance into a scientific era.

Browne's exegetical* "heresies" were triple. First: the souls of men perish with their bodies, to be later resurrected along with their corporeal substance. Second: all souls will eventually be saved, none eternally damned. Third: prayer for the dead is effective. If any discrepancy is detectable in this triad, it didn't disturb Browne. Nor did numerous other matters!

Unique was Browne's categorization of man as Amphibium: corporeal in substance and spiritual in essence. However, as anatomist he said: "Amongst all those rare discoveries and curious pieces I find in the Fabrick of Man, I do not so much content myself, as in that I find not, there is no Organ or Instrument for the rational Soul; for in the brain, which we term the seat of Reason, there is not any thing of moment more than I can discover in the crany of a beast."

As scientist and observer of what God hath wrought he further said: "Indeed, what Reason may not go to School to the wisdom of Bees, Ants, and Spiders? What wise hand teacheth *them* to do what Reason cannot teach *us*? Ruder heads stand amazed at those prodigious pieces of Nature, Whales, Elephants, Dromidaries and Camels; these, I confess, are the Colossus and majestick pieces of her hand: but in these narrow Engines there is more curious Mathematicks; and the civility of these little Citizens more neatly sets forth the Wisdom of their Maker."

In his charmingly ingenuous style he says: "I can read the History of the Pigeon that was sent out of the Ark, and returned no more, yet not question how she found her Mate that was left behind: that Lazarus was raised from the dead, yet not demand where in the interim his Soul awaited. Whether Eve was framed out of the left side of Adam, I dispute not; because I stand not yet assured which is the right side of a man, or whether there be any such distinction in Nature: that she was edified out of the Rib of Adam I believe, yet raise no question who shall arise with that Rib at the Resurrection." (Continued next issue.)

Editor's Note: Sir Thomas, though somewhat of an anatomist, may have been ignorant of the occasional supernumerary rib. Perhaps it could have given him soul saving comfort to know that the missing rib from Adam has not had to wait for the day of judgment as it has been found many times since then; perhaps Adam had the first extra one from which all others derived their genes.

Ferrous Fumarate with Ascorbic Acid in Chronic Hypoferremia

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BEUTLER ET AL.[1] state: "There are few disorders in clinical medicine in which the results of specific therapy are as dramatic and predictable as in iron-deficiency anemias." High-pressure promotion of hematinics† by pharmaceutical manufacturers, however, give the practicing physician little chance to judge objectively the numerous single and compounded iron preparations on the market. While clinicians may be aware that iron salts such as ferrous sulfate and ferrous gluconate are effective hematinics, they may not fully appreciate the reason for compounding ferrous salts with ascorbic acid. It is well established that ascorbic acid converts not only trivalent ferric iron in food into the readily absorbable bivalent ferrous form but also stabilizes the latter. Brise and Hallberg[2] showed that ascorbic acid enhances absorption of ferrous iron. Adding 500 mg. of this vitamin to 30 mg. of ferrous sulfate they noted an increase of absorption of 48 percent of this iron salt. Conrad and Shade[3] found the vitamin to form a highly soluble and readily absorbable iron-ascorbic acid chelate easily soluble at the alkaline pH in the duodenum. Luke et al.[4] described an iron-binding protein in normal gastric juice. This "gastroferrin" is decreased in iron-deficient anemias. Whether this specific protein yet to be isolated and chemically analysed combines with the iron-ascorbic acid chelate awaits further studies. These brief comments on the interrelationship between ferrous irons and ascorbic acid suggests that this vitamin plays an important role in iron metabolism.

A newcomer to the ferrous salts is "ferrous fumarate." This anhydrous salt is odorless, practically tasteless, and well tolerated. The use of this iron salt, in combination with ascorbic acid, forms the basis of this communication.

Some Chemical Aspects of Ferrous Fumarate

This anhydrous iron salt $FeC_4H_2O_4$ contains

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†See Test Your Word Score, Page 175.

about 33 percent of elemental iron. The empirical and probable structural formula of ferrous fumarate suggests that ferrous iron-fumaric acid combination is either intermolecular or polymeric. Though fumaric acid is liberated by free hydrochloric acid, the amount freed does not unduly raise the total acidity of the gastric juice. Because ferrous fumarate is not readily oxidized, the iron remains in the gastrointestinal tract, largely in the non-ionized form as shown by the equation

$$FeC_4H_2O_4 \rightleftharpoons Fe^{++} + C_4H_2O_4 =$$

The solubility of ferrous fumarate is 0.14 gm. per 100 ml. of water and 0.6 gm. per 100 ml. in 0.1 N hydrochloric acid.

Swan and Jowett[5] gave ferrous fumarate a thorough clinical trial. Administered in tablet form three times a day after meals, they found the salt to be effective in iron-deficiency anemias. Each tablet contained 200 mg. of ferrous fumarate (66 mg. elemental iron). Of 55 patients only two complained of epigastric discomfort. This occurred about 10 minutes after taking the tablets and was transitory.

Hypoferremia

The term "hypoferremia" means deficiency of iron in the blood plasma. In our institution the term covers a group of laboratory findings, namely, reduction of hemoglobin and erythrocytes below standard levels, total serum iron of less than 40 mcg. percent, serum binding capacity within and above normal, and percent iron saturation below 20. Marrow units obtained by aspiration[6] contain none to a sparse quantity of stainable iron (hemosiderin), show normoblastic hyperplasia and few to absent sideroblasts. The peripheral blood erythrocytes are characteristically deficient of hemoglobin, are microcytic, and display anisocytosis,* poikilocytosis, and some macrocytes. The reticulocyte percentage is generally within the normal range to slightly elevated. The mean corpuscular volume is below 80 cubic micra, and a mean corpuscular hemoglobin concentration of less than 30 percent. The plasma ascorbic acid level is usually below 0.7 mg. percent, and the tissue

*See Test Your Word Score, Page 175.

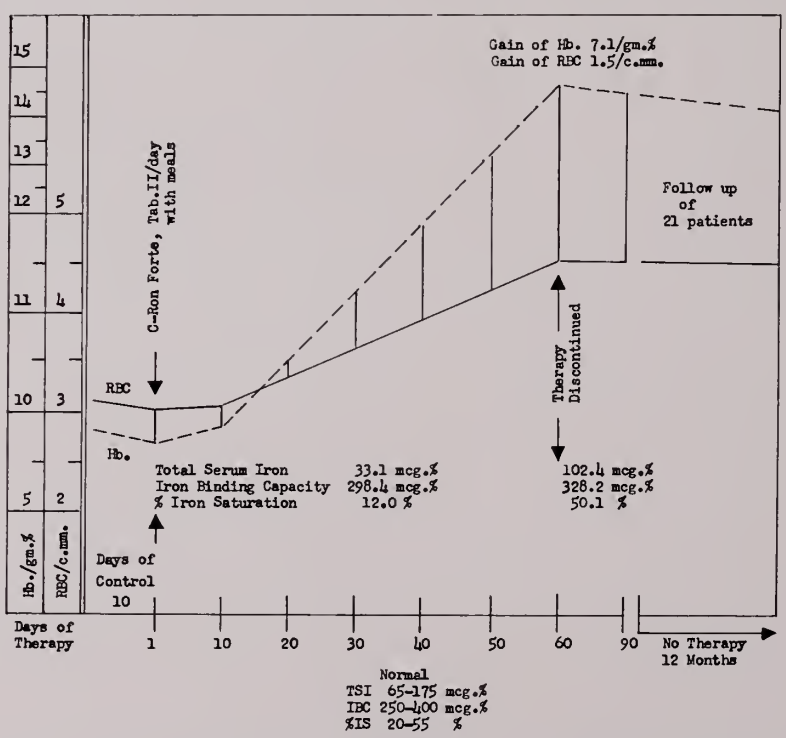


Fig. 1—Average hemoglobin and erythrocyte levels of thirty females, 14 to 42 years of age, with chronic hypoferremia and menorrhagia, measured at 10-day intervals throughout 60 days' treatment with C-Ron Forte (Rowell); and combined averages of total serum iron, iron binding capacity, and percent iron saturation at the beginning and end of therapy.

ascorbic acid subsaturation time exceeds nine minutes as determined by the Slobody method.[7]

Material and Method

Over the past four years 30 female patients, 14 to 42 years of age, who had menorrhagia of varying severity and chronicity, were seen in the Hematology Section. None had appreciable organic disease; all had "hypoferremia" as defined in this communication.

Each of these patients was placed on C-Ron Forte (Rowell) one tablet twice daily with meals. Each tablet contained ferrous fumarate 200 mg. (66 mg. elemental iron) and ascorbic acid 600 mg. The patients were followed for 90 days—a time interval suggested by Swan and Jowett. The hemoglobin and erythrocyte levels were checked every 10 days for 60 days and once at 90 days; the serum iron levels were measured at 60 and at 90 days. The individual results were then averaged and recorded. The group response levels are shown graphically in Figure 1.

None of the patients reacted adversely to the iron-ascorbic acid hematinic. Of 30 patients, 21 could be rechecked one year after therapy was discontinued. All had normal bleeding episodes, and laboratory values were within the norm.

Comment

Taymor et al.[8] state: "Depletion of tissue iron is the more important factor in the production of menorrhagia rather than anemia." This opinion is well supported by our studies of the cause of chronic hypoferremia. Though Swan and Jowett demonstrated that a daily dose of 600 mg. of ferrous fumarate is effective in uncomplicated iron deficiency, it is my belief that a combination of ferrous fumarate 200 mg. and ascorbic acid 600 mg. is sound, Israëls and Simmons,[9] working with a controlled-release ferrous sulfate-ascorbic acid preparation, said: "Ideally, 700 mg. ascorbic acid should be included in the tablet." While this amount of ascorbic acid seems to be extraordinarily large, one must keep in mind that this vitamin is essential for iron metabolism and the fact that chronic hypoferremia is often complicated by subclinical scurvy.

Fujino et al.[10] noted during normal menstruation a reduction of as much as 13 percent in the plasma ascorbic level. It is noteworthy that Junghans,[11] by giving parenteral ascorbic acid, successfully controlled gynecological bleeding disorders. I have studied patients who had an unsuccessful cervical dilatation and curettage for menorrhagia, an ascorbic acid plasma level of less than 0.7 mg. percent, a tissue saturation in the subclinical scurvy range, a moderate hypochromic-normocytic anemic state, and a low normal serum iron level. These patients benefited from 2000-3000 mg. of ascorbic acid given daily by mouth until the tissue saturation was within the norm.

Summary

Thirty female patients, 14 to 42 years old, who had hypoferremia and menorrhagia of varying severity and chronicity, were successfully treated with C-Ron Forte (Rowell) tablets, one twice daily with meals, and their hypoferremia was alleviated within sixty days. No undue gastrointestinal disturbances to the hematinic were observed. The average response of the thirty female patients is presented in Figure 1.

Acknowledgment

Thanks are extended to the members of our medical staff who referred patients to the Hematology Section for this research problem, and to the personnel of the clinical laboratory of our institution for their cooperation. I am indebted to Dr. B. E. Greenwell, Rowell Laboratories, Baudette, Minnesota for supplying C-Ron Forte.

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To be rich in friends is to be poor in nothing.—Lilian Whiting.

The Ailments of Men in History

Arteriosclerosis, high blood pressure, hyperpiesis,* and chronic Bright's disease —all more or less names for the same thing, or at any rate for cognate disorders— form one of the great tragedies of the world. They attack the very men whom we can least spare; they are essentially the diseases of statesmen. Although these diseases have been attributed to many causes—that is to say, we do not really know their true cause—it is certain that worry has a great deal to do with them. If a man be content to live the life of a cabbage, eat little, and drink no alcohol, it is probable that he will not suffer from high blood-pressure; but if he is determined to work hard, live well, and yet struggle furiously, then his arteries and kidneys inevitably go wrong and he is not likely to stand the strain for many years. Unless a politician has an iron nerve and preternaturally calm nature, or unless he is fortunate enough to be carried off by pneumonia, then he is almost certain to die of high blood-pressure if he persists in his politics. I could name a dozen able politicians who have fallen victims to their political anxieties. The latest, so far as I know, was Mr. John Storey, Premier of New South Wales, who died of high blood-pressure in 1921; before him I remember several able men whom the furious politics of that State claimed as victims. In England Lord Beaconsfield seems to have died of high blood-pressure, and so did Mr. Joseph Chamberlain. Mr. Gladstone was less fortunate, in that he died of cancer. He must have possessed a calm mind to go through his furious strugglings without his kidneys or blood-vessels giving way; that, and his singularly temperate and happy home-life, preserved him from the usual fate of statesmen.

Again, when we consider that the destinies of nations are commonly held in the hands of elderly gentlemen whose blood-pressures tend to be too high owing to their fierce political activities, it is not too much to say that arteriosclerosis is one of the greatest tragedies that afflicts the human race. Every politician should have his blood-pressure tested and his urine examined about once a quarter, and if it should show signs of rising he should undoubtedly take a long rest until it falls again; it is not fair that the lives of millions should depend upon the judgment of a man whose mind is warped by arteriosclerosis.†

*See Test Your Word Score, Page 175.

†C. Mac Lauren: Post Mortems of Mere Mortals, 1925.

Editor's Note: I cannot believe that it is the over-work that kills a man so much as dissipations—they can be many and varied; worry and apprehension are no doubt often associated and play a part, but attributing organic disease to hard work is, I fear, post-hoc reasoning. Gladstone died at the ripe age of 89. Throughout his life he maintained moderation in everything but work. Reference: John Morley's Life of Gladstone, 1903.

On Vomiting

That vomiting is of most service which consists of phlegm and bile mixed together, and neither very thick nor in great quantity; but those vomitings which are more unmixed are worse. But if that which is vomited be of the color of leeks or livid, or black, whatever of these colors it be, it is to be reckoned bad; but if the same man vomit all these colors, it is to be reckoned a very fatal symptom. But of all the vomitings, the livid indicates the most imminent danger of death, provided it be of a fetid smell. But all the smells which are somewhat putrid and fetid, are bad in all vomitings.*

*Hippocrates: The Book of Prognostics.

Heinecke-Mikulicz vs Finney Pyloroplasty

Identical Procedures — Different Vintage

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VAGOTOMY COMBINED with pyloroplasty has gained acceptance as an operation for duodenal ulcer. Some surgeons say they prefer either a Heinecke-Mikulicz pyloroplasty; others indicate they prefer a Finney pyloroplasty, and both refer to them as functionally different procedures. The proponents of the latter procedure may refer to a "gastroduodenostomy of the Finney type;" they emphasize the great width of its anastomosis, pointing out that Finney recommended a long incision through the pylorus and duodenum with a transverse closure.

In evaluating drainage procedures after vagotomy Bryant and co-workers[1] state: ". . . the recurrence rate of the Heinecke-Mikulicz pyloroplasty is almost three times the rate of the Finney pyloroplasty. The Finney procedure creates an opening between the stomach and duodenum several centimeters larger and in a more side-to-side fashion than the Heinecke-Mikulicz pyloroplasty." More recently a study of 48 consecutive patients with peptic ulcer comparing the two procedures at random found equally good results with both.[2] Because of these contradictory reports, I have tried to find how the two operations differ anatomically. Unless one chooses to call a large Heinecke-Mikulicz procedure a Finney pyloroplasty, I believe the two procedures are basically the same.

Confusing Factors

Readers may have misinterpreted the original description of the procedures. The illustrations were not wholly self-explanatory, and the proponents of either procedure may have had a preconceived idea of what each ought to accomplish. Therefore they look at their work from different viewpoints, and the medical artist can make the same pyloroplasty as a sharply-angled gastroduodenostomy or as a transverse closure of a longitudinal slit through the pylorus (Figures 1 and 2).

The Surgeon's Viewpoint

In 1886 a report of pyloroplasty performed by Heinecke, professor of surgery at the University of Erlangen, appeared in the doctoral thesis of a candidate, Fronmüller.[3] Mikulicz, then professor of surgery at the University of Königsberg, published and popularized this procedure in 1888,[4] giving Heinecke credit. It consists of a longitudinal incision of all layers of the stenosed pylorus and a transverse closure.

Finney, working in Baltimore, described in 1902[5] a "horseshoe"-shaped incision through the pylorus followed by a transverse closure in layers. He stated: "Upon the thoroughness with which the pylorus, lower end of the stomach, and upper end of the duodenum are freed depends, in large measure, the success of the operation and the ease and rapidity of its performance. . . . The incision is made in the shape of a horseshoe. In all of my cases the incision has been about 12 cm in length and could have been made longer, had I chosen to make it so."

The "horseshoe" incision would seem to be merely a longitudinal incision traversing the bend of the duodenum which, if straightened out, would be longitudinal along the anterior aspect. Transverse closure of the long "horseshoe" incision without releasing the duodenum might seem to differ from a Heinecke-Mikulicz procedure if it is merely folded over and closed. But if one visualizes it as a longitudinal incision and transverse closure after releasing the duodenum, it seems to constitute the same procedure as the Heinecke-Mikulicz pyloroplasty.

Jaboulay[9] reported the first gastroduodenostomy in 1892 in which he mobilized the duodenum, preceding Kocher's description[10] by 11 years. He then anastomosed the antrum with the duodenum, thus bypassing the pylorus.

Mobilization of the duodenum, popularly known as the Kocher maneuver, gives the pyloroplasty more of a "Finney-like" appearance; it relieves the tension in the center of the suture line.

Little has been added to pyloroplasty since

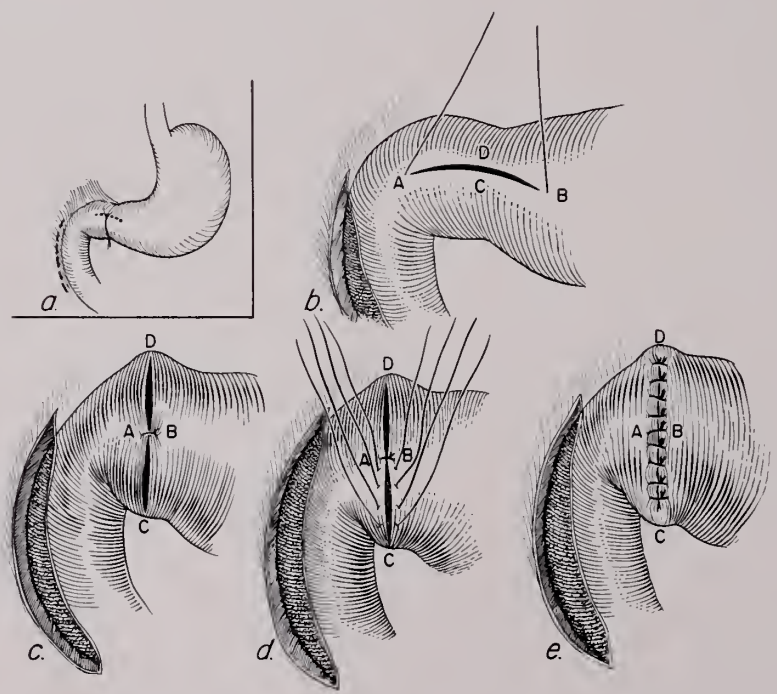


Fig. 1—Heinecke-Mikulicz pyloroplasty. The longitudinal pylorotomy is about 6 cm long. The distant points A and B are approximated at the mid point in the transverse closure of the incision. Point C, the cut edge of the pylorus, has a tendency to stick out as a "dog ear." Note that the duodenal mobilization by a Kocher maneuver facilitates the transverse approximation.

the principle of longitudinal incision and transverse closure was first established by Mikulicz. Fredet[6] in 1908 and Weber[7] in 1910 described longitudinal pyloromyotomy, confining the incision to the seromuscular layer and closing it transversely. Both authors noted the difficulty of reapproximating the cut edges in the transverse direction, and Fredet found it impossible to close the mid-portion of the incision. Ramstedt[8] performed for the first time a pyloromyotomy without closure of the seromuscular coat in 1912.

Judd[11] in 1922, Horsley[12] in 1926 and Beattie[13] in 1950 advocated pyloroplasty including full thickness excision of the stenosing pyloric ulcer. Judd's pyloroplasty, first performed in 1920, enjoyed great popularity for about 12 years as a duodenal ulcer operation.

Pyloroplasty, when done for peptic ulcer in conjunction with vagotomy, has a threefold purpose: it disables the pyloric sphincter, widens the gastric outlet, and gives surgical access to the ulcer. An operation which does this and consists of longitudinal incision and transverse closure of the pyloric region was first described by Heinecke and Mikulicz. It therefore seems unjustified to call a long pyloric incision a Finney pyloroplasty. Duodenal mobilization should probably be performed in most vagotomy-pyloroplasty cases.

Conclusions

Because the Heinecke-Mikulicz pyloroplasty predates Finney's report of pyloroplasty by 16 years and because both procedures are basically identical, the term "Finney pyloroplasty" should be abandoned.

References can be secured from the author or the reprints.

Reprint requests: 1224 Metropolitan Medical Center, Minneapolis.

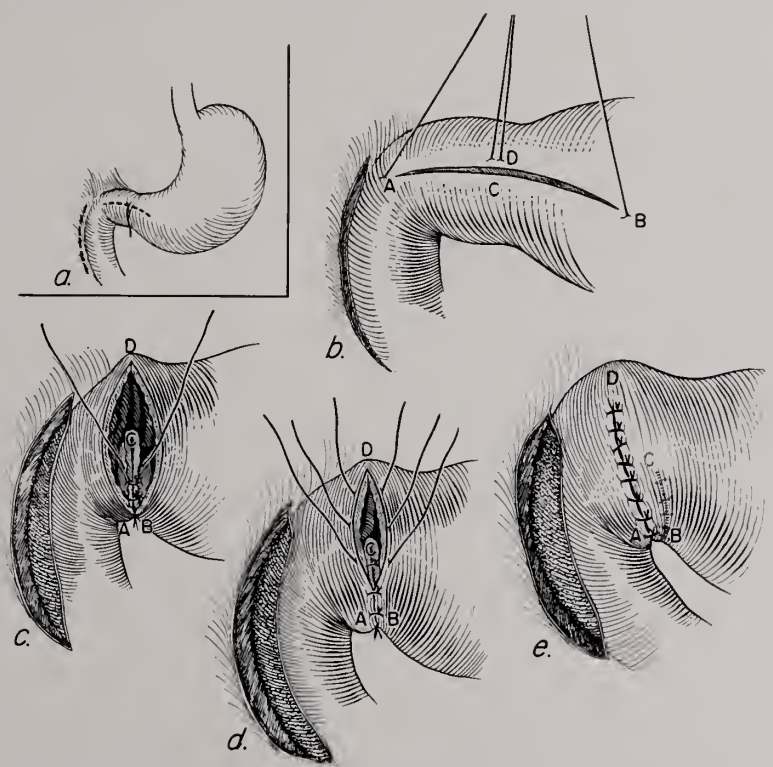


Fig. 2—So-called Finney pyloroplasty: The incision is about 10 cm long. In order to show the similarity with the Heinecke-Mikulicz pyloroplasty the gastroduodenal angle and the extent of duodenal mobilization are almost identical with those seen in Figure 1. The "dog ear" C, however, has disappeared into the lumen and posteriorly, principally because of the longer incision (and could be easily pushed out). This feature of the hidden lower angle accounts largely for the notion that the Finney pyloroplasty differs in principle from the Heinecke-Mikulicz pyloroplasty, though in reality they are essentially identical.

I believe in getting into hot water. It keeps one clean.—G. K. Chesterton

St. Leonard's Hospital, York



Ruins of St. Leonard's Hospital, York. Courtesy of City of York Information Service.

The first hospitals in England were built by the Romans. Of the early Saxon hospitals, however, one of the first was founded at York in 937 A.D. by King Athelstan and dedicated to St. Peter. It burned in the twelfth century and was rebuilt as St. Leonard's Hospital by King Stephen.

Like most medieval hospitals, it served not only the sick but any needy persons seeking shelter and sustenance. Loaves and fishes were distributed daily to any who appeared at the gate. Special dinners were served on Sundays. The hospital became the largest in the country, housing on Easter of the year 1370 224 sick and poor besides 23 orphan boys for whom it provided home and school.

St. Leonard's differed from many medieval hospitals in that it was essentially a secular institution, although bearing a strong religious influence. An important source of its support was a tax, the "thraves* of St. Leonard's," which provided that a specified number of sheaves of grain were to be given to the hospital from each plow working in the Archdiocese of York. The "thraves" belonged to St. Leonard's by virtue of King Athelstan's gift which in turn had been granted to him by his northern subjects in recognition of his destruction of wolves that prowled the countryside.

King Henry III gave royal support to St. Leonard's in the form of permission "to take what they need in the forest of Yorkshire for building and burning, and also of herbage and pasture for flocks and anything needful for their ease." Another source of revenue was "sepulture" by which the institution received fees and legacies from the burial of benefactors.

The hospital required a large staff which included sisters, monks, and priests as well as lay brothers. There were three chapels. Rules of the hospital stipulated that "when the master is a layman, he shall wear the habit of the house." The strong religious tradition, as well as the fact that much of the hospital's property had actually been accumulated from gifts to the clergy, led to frequent disputes between Church and Crown regarding ownership of the institution. In 1246 a jury decided in favor of the Church, but subsequently the Crown recovered the hospital once again. The dispute ended once and for all in 1537 when Henry VIII closed the hospital and seized its property.

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*See Test Your Word Score, Page 175.

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Rheumatoid Disease

Adrenocortical Function and Intermittent Steroid Therapy

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THE RHYTHMIC PRODUCTION of cortisol (hydrocortisone) by the adrenal cortex has been long appreciated,[1] but only recently have serious attempts been made to derive practical therapeutic advantage from this natural phenomenon. Every-other-day administration of prednisone has been suggested as a means of minimizing the undesirable side effects of long-term steroid therapy in allergic asthma and childhood nephrosis. Harter[2] reported data showing minimal or no adrenocortical suppression in patients given prednisone on an alternate-day regimen. Ackerman and Nolan[3] reported near normal rises in plasma 17-hydroxycorticosteroids following insulin stimulation in a group of 10 patients who were on alternate-day steroid therapy (average rise 15.1 μg) as compared with a group of eight patients on divided daily doses (average rise 4.8 μg). Soyka and Saxena[4] presented clinical data showing rather striking reversal of cushingoid changes in nine nephrotic children who were changed from daily multidose therapy to the same total steroid given as a single dose every 48 hours. Studies of 17-hydroxycorticoid excretion and serum cortisol levels done in two of their patients showed no suppression of the pituitary-adrenal axis. Based on data from a short-term study of adrenocortical function in six normal males given triamcinolone, Grant[5] et al. suggest that the best method of steroid administration for control of clinical symptoms, and causing least adrenal suppression, is an every AM schedule.

In contrast to these reports, Siegel et al.[6] found significant adrenocortical suppression in all of 10 asthmatic subjects after three weeks of betamethasone given in a dosage of 3 mg. every other day. Harter et al.[7,8] stated that the advantages of alternate-day therapy with prednisone cannot be extended to the longer-acting steroid analogs. In a recent review by Ney,[9]

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the limitations of the data thus far published are pointed out, and he warns against the greater license in the use of steroids on the presumption of the greater safety of the alternate-day regimen.

Intermittent adrenal corticosteroid administration by "blocks" of time, such as three days on therapy followed by four days off therapy, was reported as reducing untoward side effects in juvenile rheumatoid arthritis and as maintaining adrenocortical responsiveness.[10] A similar schedule of therapy in adult nephrosis showed essentially unchanged adrenocortical function after 12 to 18 months' therapy, and the authors felt that the expected side effects were diminished.[11]

Rheumatoid arthritis, because of its frequent failure to respond to more conservative measures, may cause the physician to employ long-term steroid therapy. This makes any advantage of intermittent therapy of considerable importance to such patients, especially since there is a common clinical impression that the rheumatoid arthritic is more vulnerable to the toxic side effects of adrenocortical steroids. Therefore, it was decided to study a group of rheumatoid patients in order to obtain possible answers to the following questions: (1) Can intermittent therapy maintain as good clinical control of the patient as the traditional daily multi-dose schedule? (2) Can clinical signs of steroid toxicity be lessened on the intermittent schedule? (3) Can adrenocortical suppression be lessened by intermittent therapy? (4) Is there a difference between the short-lived steroids prednisone-prednisolone and the longer-acting analogs—in this case dexamethasone?

Materials and Methods

Fifteen patients were selected for this study: 13 had classical rheumatoid arthritis, one had rheumatoid arthritis with rheumatoid (Ankylosing) spondylitis, and one had systemic lupus erythematosus. All but two patients were on some form of adrenocortical steroid therapy at the start of the study. All were admitted to the hospital for the metyrapone (Metopirone CIBA) tests. After at least 48 hours of no steroid (one month in the case of the patient who had been on parenteral steroid therapy) a control 24-hour urine sample was collected. Oral metyrapone was then given in a dosage of 750 mg. every four hours for six doses, and 24-hour urine collections were continued for the second and third days. Aliquots of each 24-hour urine collection were frozen and subsequent 17-hydroxycorticoid (17 OHCS) determinations were done by a modification of the method of Silber and Porter.* The patients were then given oral dexamethasone according to one of two schedules: The estimated daily steroid requirement for clinical control of the patient's disease was divided into two equal parts and given twice a day at 8 AM and 8 PM; or twice this daily amount was administered as a single dose the first thing in the morning of every other day. After two months the patient was admitted to the hospital for a repeat metyrapone test and then started on two months of the other dosage schedule. After the third metyrapone test nine of the patients were further studied by changing their steroid to an equivalent dosage of prednisone or prednisolone which was given for about three months on either an every-other-day or an every-morning schedule. Six of these patients were then continued on the intermittent schedule for an additional 10 to 12 months, following which a fifth metyrapone test was done. Complete physical examinations and routine laboratory studies were performed on each hospital admission. In addition, certain laboratory studies were done at the time of the outpatient visits which were at intervals of one to four weeks.

Results

The essential data of the study are presented in Table 1. Several things may be called to the reader's attention. The three patients (Cases 3, 4 ,5) who had initially been on intermittent prednisone-prednisolone all had normal control metyrapone tests despite at least seven months of prior steroid. Yet one patient (Case 9) who had been on only five months of daily multidose prednisone showed significantly decreased 17-hydroxycorticoid output. Rather surprisingly, the two patients (Cases 7, 8) who had been on long-term twice-a-day methyl prednisolone showed good control 17-hydroxycorticoid values in contrast to the expected depressed adrenocortical function shown by the two patients (Cases 10, 13) who had been on dexamethasone or betamethasone for comparable periods. A fifth patient (Case 6) who had been on one of the long-acting steroids (betamethasone) for several years on a once-a-day AM schedule also showed depressed 17-hydroxycorticoid output.

Intermittent dexamethasone failed to improve 17-hydroxycorticoid output over values obtained following daily multidose therapy in 13 of the 15 patients (Table 2). Of the two cases in which significant improvement was found, one (Case 2) had been on intramuscular

*The author wishes to express his thanks to Dr. J. C. Melby, Head of the Section of Endocrinology, Boston University Medical Center, Boston, Mass. who did all of the 17-OHCS determinations in this study.

TABLE I

Pt.	Sex	Age	Dx.	Duration	Pre-Study Steroid Therapy	24 Hour Urine Mgs. of 17 OHCS	Dexamethasone Steroid Rx
1	M	56	R.A.	18 mos.	2 mos. Triamcinolone 4-6 mg. daily (2xday)	12 19*(12-15-64) 59	1.5 2xday
2	F	53	R.A.	8 yrs.	2 yrs. Triamcinolone or 6-methyl prednisolone 30-40 mg. I.M. every 3 wks.	4 4*(1-15-65) 13	1.5 EOD
3	M	67	R.A.	18 mos.	8 mos. Prednisone 5-10 mg. daily (in evening)	8 17*(1-6-65) 19	1.0 EOD
4	M	70	R.A.	10 yrs.	7 mos. Prednisolone 20 mg. EOD start 6-1-64 15 mg. EOD start 7-15-64	8 24*(1-6-65) 27	0.5 2xday
5	F	31	R.A.	2 yrs.	7½ mos. Prednisone 10 mg. EOD	5 9*(1-16-65) 29	0.375 2xday
6	F	42	R.A.	18 yrs.	10 yrs. Var. steroid-mostly 0.6 mg. betamethasone (in A.M.)	3 2*(1-21-65) 4	1.5 EOD
7	F	24	R.A.	5½ yrs.	5 yrs. 6 Methyl prednisolone 4 mg. daily (2xday)	6 12*(2-18-65) 22	1.5 EOD
8	M	46	R.A.	3½ yrs.	2 yrs. 6 Methyl prednisolone 6-8 mg. daily (2xday)	7 13*(2-20-65) 25	3 mg. EOD reduced to 2.25 EOD on 3-9-65
9	F	32	L.E.	12+yrs.	5 mos. Prednisone 15-40 mg. daily (4xday)	<1 2*(12-14-64) 7	1.5 EOD
10	F	38	R.A.	12 yrs.	3 yrs. Betamethasone 0.6 mg. daily (2xday)	2 3*(12-30-64) 3	1.5 EOD
11	F	51	R.A.	25 yrs.	None	5 16*(1-16-65) 24	0.375 2xday
12	F	53	R.A.	26 yrs.	8 yrs. Prednisone 5-10 mg. daily (3xday)	5 7*(1-22-65) 7	1.5 EOD
13	F	56	R.A.	15 yrs.	4 yrs. Betamethasone or dexamethasone 0.6-0.75 mg. daily (2xday)	<1.0 2.0*(1-13-65) 3.0	1.5 EOD
14	F	47	R.A.	6 yrs.	None	<1.0 1.0*(12-28-65) 10	0.75 2xday
15	F	61	R.A. & R.S.	39 yrs.	2½ mos. Prednisone 10 mg. daily (2xday)	8 12*(2-10-65) 21	3 mg. EOD

*Day of Metyrapone

**EOD = every other day.

TABLE I (Extended)

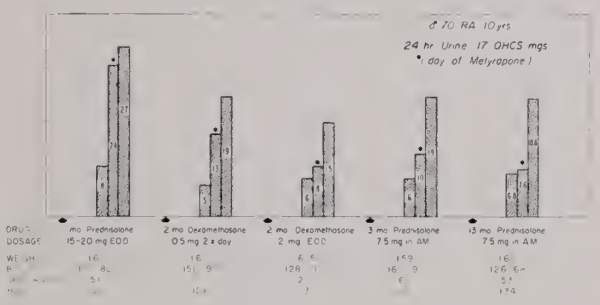
Urine Mgs. of 17 OHCS	Dexamethasone Steroid Rx	Urine Mgs. of 17 OHCS	Prednisone-Prednisolone Steroid Rx	Urine Mgs. of 17 OHCS-Short Term Study	Urine Mgs. of 17 OHCS-Long Term Study
9 18*(2-16-65) 49	6 mg. EOD**	3 10*(4-20-65) 22	Prednisone 15 mg. in AM start 8-4-65 20 mg. in AM start 10-13-65	7 16*(11-13-65) 27	
2 5*(3-19-65) 21	0.375 2xday	1 1*(5-14-65) 3	Prednisolone 15 mg. EOD start 7-30-65	4.0 5.4*(10-29-65) 11.3	3.6 0.0*(11-11-66) 21.7
9 14*(2-22-65) 19	0.25 2xday	5 8*(4-26-65) 16			
5 13*(3-6-65) 19	2 mg. EOD	6 8*(5-13-65) 15	Prednisolone 7.5 mg. in AM start 7-27-65	6 10*(10-19-65) 19	6.8 7.6*(8-30-66) 18.8
4 6*(3-21-65) 14	1.5 EOD	3 5*(5-29-65) 15	Prednisone 10 mg. EOD start 7-6-65	5.1 8.5*(11-6-65) 9.8	4.4 7.0*(9-3-66) 16.9
1 2*(3-30-65) 3	0.375 2xday	<1 <1*(5-30-65) 3	Prednisone 7.5 mg. in AM start 7-26-65	1.2 2.0*(10-22-65) 6.3	1.3 2.0*(9-16-66) 2.9
4 6*(4-21-65) 9	0.375 2xday	1.0 3.0*(6-30-65) 2.0	Prednisone 10 mg. in AM start 8-2-65	4.2 4.0*(11-3-65) 12.1	
4 5*(5-13-65) 4			Prednisone 15 mg. EOD start 7-26-65	8.0 8.4*(11-6-65) 29.0	2.5 15.7*(8-27-66) 13.3
1 4*(2-13-65) 14	0.375 2xday	2 3*(4-23-65) 9			
<1 2*(3-5-65) 1	1.5 EOD	1 1*(5-17-65) 1			
2 10*(3-22-65) 18	1.5 EOD	8.0 18.0*(6-27-65) 16.0			
3 2*(3-25-65)+ 9 +(lost 150 cc urine)	0.375 2xday	2.0 3.0*(7-12-65) 3.0			
1 3*(4-30-65) 2			Prednisone 7.5 mg. in AM start 9-1-65	1.4 1.4*(11-28-65) 4.2	0.8 1.8(10-4-66) 3.9
4 7*(4-1-65) 6	3.0 EOD	2 3*(6-3-65) 7	Prednisone 20 mg. EOD start 9-22-65	3.3 4.0*(1-13-66) 6.1	
5 11*(4-20-65) 13					

steroid therapy, and the other (Case 9) was the patient with lupus erythematosus who had been on gradually decreasing doses of prednisone from an initial dose of 40 mg./day needed to control a lupus flare. Both of these patients showed evidence of adrenocortical suppression when their dexamethasone was changed to twice-a-day administration.

Of the eleven patients who had a two-month trial on the twice-a-day dexamethasone schedule, only one (Case 1) failed to show significant adrenocortical suppression. However, this patient then did show decreased 17-hydroxycorticoid output when continued for two months on dexamethasone given on the every-other-day schedule.

Of the nine patients who were continued on the study by a later change to intermittent (every AM or every other day) prednisone or prednisolone, six showed an increase in 17-hydroxycorticoid output and three were unchanged at the three-month study period (Table 3). (The 17-hydroxycorticoid determinations were not done immediately before the start of intermittent prednisone-prednisolone. The last values of the dexamethasone study were used as the comparative "baseline." Since all patients were continued on dexamethasone until the start of prednisone-prednisolone, their metyrapone tests, based on each patient's previous response, would have been unlikely to show improved adrenocortical function.) Six of these nine patients were further continued on the intermittent prednisone-prednisolone schedule for 10 to 12 months. Five either maintained or improved their 17-hydroxycorticoid output; only one showed a moderate decrease (Table 3). The Figure is a graphic illustration of the data in Case 4. This patient had a normal metyrapone test after seven months of prednisolone therapy which was given on an every-other-day dosage basis; a change to twice-a-day dexamethasone caused a significant drop in 17-hydroxycorticoid excretion, which declined further despite a change to every-other-day administration. When changed back to intermittent prednisolone, however, there was improvement in 17-hydroxicorticoid excretion after three months, which was essentially maintained after an additional 10 months of once-a-day prednisolone therapy.

Certain significant clinical features of the intermittent and twice-a-day schedules are noted in Tables 4 and 5. Almost all patients had more arthritic complaints during the initial days of the every-other-day dexamethasone as compared with the twice-a-day schedule. In only a few patients was this reflected by an objective increase in joint swelling or tenderness or by a rise in sedimentation rates; and "tolerance" to the intermittent dosage developed within one month in seven of the patients. Yet eight patients expressed a continued preference for the twice-a-day schedule. One patient (Case 1) took



Figure

TABLE 2

17-OHCS Excretion Following EOD* Dexamethasone

Improved (compared with daily multidose period)	2 Patients
Decreased	6 Patients
No Change	7 Patients

*Every other day

TABLE 3

17-OHCS Excretion Following Intermittent Prednisone—Prednisolone

Short term (3 months) study: 9 patients	
Improved (compared with dexamethasone period)	6 Patients
No change	3 Patients
Long term (one plus year) study: 6 patients	
Improved (Compared with end of 3 mo. Prednisone-Prednisolone period)	1 Patient
No change	4 Patients
Decreased	1 Patient

TABLE 4

Patient Preference of Dosage Schedule

Preferred intermittent RX	None
Preferred 2xday RX	8 Patients
Noticed little or no difference	7 Patients

TABLE 5

Patient Tolerance to Steroid Withdrawal

Better tolerance following 2xday RX	None
Better tolerance following intermittent RX	7 Patients
Noticed little or no difference	8 Patients

until noon to get out of bed each day while on intermittent dexamethasone, and he became almost bedridden when changed to intermittent prednisone therapy due to the fewer hours of daily arthritis relief. He was much improved when changed to twice-a-day prednisone administration.

During the necessary abrupt steroid withdrawal prior to each metyrapone test, all patients experienced an increase in arthritic symptoms; yet no serious indications of adrenocortical insufficiency appeared. Eight of the 15 patients found that this period of withdrawal was more easily tolerated following the intermittent schedule as compared with the twice-a-day trial.

There were no consistent differences between the twice-a-day and the every-other-day schedules with respect to the routine laboratory tests, or the patients' weights and blodo pressures. The physical signs of chronic steroid administration were not prominent in this group, but there did appear to be a reduction in the cushingoid facies of two patients while on the every-other-day trial: in one patient after two months, and in the second patient after four months. Of the six patients who were continued on intermittent prednisone-prednisolone for over one year, only one patient (Case 13) had significant signs of hypercortisonism in the form of easy bruising and gross cushingoid facies. She also developed a gastric ulcer in the 12th month and an additional vertebral compression fracture in her 13th month of intermittent therapy!

Summary

Adrenocortical function was studied through the use of the oral metyrapone test in 15 patients who had been on no (two patients) or on various cortisol derivatives (13 patients) and were then placed on a single cortisol derivative-dexamethasone. All patients had at least a two-month trial of dexamethasone on an every-other-day dosage schedule, and 11 patients had at least a two-month trial of dexamethasone given on a twice-a-day dosage schedule. Nine patients were further studied after a change to prednisone or prednisolone on a once-a-day or every-other-day dosage schedule for about three months; six of these patients were still further studied after an additional 10 to 12 months of their intermittent schedule.

Dexamethasone, a long-acting steroid analog, failed to improve 17-hydroxycorticosteroid excretion despite the alternate-day dosage administration in 13 of the 15 patients and actually caused further suppression in six. Still greater suppression, however, was evident with the twice-a-day dexamethasone dosage.

When nine patients were changed to the short-acting steroids, prednisone or prednisolone, on an every-other-day or a once-a-day (AM) dosage schedule, 17-hydroxycorticoid excretion improved in six and was unchanged in three after an average of three months' therapy. And when six of these nine patients were continued on this same intermittent schedule for an additional 10 to 12 months, 17-hydroxycorticoid excretion improved or remained unchanged in five and showed a modest fall in only one patient.

Conclusions

These data point to a definite preference for the use of the short-acting adrenocorticosteroids on an every AM or every-other-day dosage schedule as a means of minimizing adrenocortical suppression. The clinical control of the patients' symptoms was more difficult on intermittent steroid therapy, but most patients developed a tolerance to the initial "swings" in their arthritic symptoms, and in only one patient was it necessary to return to the twice-a-day dosage schedule in order to regain adequate symptomatic control. The data did not indicate significant differences in the clinical signs of steroid toxicity when patients were on the different dosage schedules.

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2. Harter, J. C., Reddy, W. J., and Thorn, G. W.: Studies on An Intermittent Corticosteroid Dosage Regimen. New Eng J Med 269:591, 1963.
3-11. May be secured from the author or the reprints.

The pot boils, friendship lives.—Ancient Greek Proverb.

An Oral Combination of Antihistamines and Nasal Decongestants

Evaluation of

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ANTIHISTAMINES PRODUCE their characteristic effects by competing with histamine for the cell receptor. If the number of histamine molecules exceeds the number of antihistamine molecules, antihistamines do not act effectively.

Yet the dose of an antihistamine is frequently limited because of the side effects. In other words, the dose needed to control the allergic symptoms often so sedates the patient or produces such side effects that the therapeutic value of the medication cannot be attained.

The side effects of the antihistamines vary considerably from one chemical group to another. The ethanolamines, ethylene diamines, and phenothiazines characteristically cause sedation and even sleep in some people. Propylamines usually cause only mild if any drowsiness. A number of antihistamines produce gastrointestinal distress. The ethanolamines cause minimal gastrointestinal symptoms due to their anticholinergic quality. The toxic responses to antihistamines have been reported many times and need little comment.

Antihistamines find their greatest usefulness in the symptomatic treatment of allergic rhinitis. When this illness is mild, a great many patients experience relief, but some cases do not respond sufficiently to the maximum tolerated doses. A tolerance to antihistamines can be induced by regular use. A given antihistamine becomes less effective in controlling symptoms after repeated administration; thereafter the usual therapeutic dose loses its value.

The chronic allergic rhinitis patient responds less effectively to antihistamines than the acute seasonal case; however, the former will often receive relief if the dose is increased.

Material and Method

Incorporating a sympathomimetic drug often helps to relieve some of these patients. There are many antihistamine combinations available.

*Clinical Staff, University of Minnesota Medical School and St. Barnabas Hospital of Minneapolis.

Some of these preparations incorporate stimulants to counteract the sedative effect; others use bronchodilators, decongestants, and even corticosteroids.

The Oral Prescription

The preparations we have considered contain four drugs. A study was designed to evaluate this combination of four drugs in office practice.

Chlorpheniramine Maleate (Chlortrimeton)	4 mg.
Tripelennamine HCl (Pyribenzamine)	50 mg.
Phenylpropanolamine HCl (Propadrine)	25 mg.
Phenylephrine HCl (Neosynephrine)	10 mg.

Phenylephrine and phenylpropanolamine are sympathomimetic drugs and are primarily alpha receptor in their activity. Phenylephrine is a good nasal decongestant with some pressor* and vasoconstrictor effects; phenylpropanolamine is also a nasal decongestant with some bronchodilator and vasopressor effects. Both agents are mild stimulants.

Incorporating four drugs into one tablet gives the advantage of two antihistamines in therapeutic doses. The sedative qualities are offset by the stimulating effect of the sympathomimetics. In addition, there is a mild decongestant and bronchodilator reaction.

The pressor effects indicate that these drugs should be used with caution in patients with hyperthyroidism, hypertension, some cardiac conditions, glaucoma, and related conditions.

In general, all of the patients in this group have chronic allergic rhinitis problems. Most of the cases had poor results with antihistamines alone. The results demonstrated in this study represent a refractory group and not the random allergic population.

Questionnaire

The drug† was given to 87 patients along with a questionnaire to record effectiveness and side effects. After a trial of medication, the questionnaire was reviewed with the patient, and the subjective and objective factors were carefully assessed.

*See Test Your Word Score, Page 175.

†Prepared by and supplied through the generosity of the Rowell Laboratories, Inc., Baudette, Minnesota.

TABLE 1
Age and Sex Distribution

	Females	Males
9-16 years of age	7	8
17-45 years of age	24	16
46-66 years of age	17	15

Results

All of these patients had perennial allergic rhinitis, often with other manifestations of allergic disease. Many were also receiving allergic hyposensitization as well as various treatments for their other allergic manifestations.

Synergistic Action

TABLE 2
Effectiveness of Medication

Better than previous medication	30
As good as and maybe better than previous medication	11
As good as previous medication	22
Not as good as previous medication	17
No help from medication	7

There seems to be a synergistic action when these two antihistamines are combined with two sympathomimetic agents. This is evidenced by the fact that 63 patients or approximately 72% of those studies experienced relief as great as or better than previous medication.

Side Effects

Fifty-six of the patients had no significant side effects. Thirty-one reported irritating side effects. Five reported more than one side effect. Some patients complained of drowsiness, gastric distress, and lightheadedness which subsided with continued medication. Gastric distress was usually alleviated by taking tablets with or after meals. The most common side effects are tabulated in Table 3.

TABLE 3
Side Effects

Drowsiness	9
Gastric distress	9
Lightheadedness	4
Excessive dryness	2
Dizziness	2
Headaches	4
Nausea	1
Nervousness	1
Shortness of breath	1

The incidence of side effects in this group of

patients is higher than in most studies on antihistamines. This increase is undoubtedly due to the fact that this tablet represents the usual therapeutic dose of two antihistamines, so that the cumulative pharmacologic side effects would also be increased.

Children experienced (or reported) fewer side effects than adults. Women experienced more side effects than men. The oldest age group had a higher incidence than the middle-age group.

Summary

A preparation containing two antihistamines and two sympathomimetic agents was clinically evaluated in 87 patients.

This study indicates that this combination gives relief to some of the patients who obtain no relief from antihistamines given singularly.

The side effects experienced are similar to those encountered with all antihistamines and sympathomimetic combinations. The increased number of side effects are due to the cumulative pharmacological side effects of the various components.

Nobel Prize Winners in Medicine and Physiology

George Von Bekesy 1961

For his discoveries concerning the physical mechanisms of stimulation within the cochlea.

Von Bekesy's researches into the sound-transmitting mechanics of the inner ear originated in and was based on his observations of the operation of the Hungarian telephone system after World War I.

In his "Concerning the pleasures of observing, and the mechanics of the inner ear," Les Prix Nobel en 1961, he said:

"After the First World War, the only place in Hungary that had some scientific instruments left and was willing to let me use them was the research laboratory of the Post Office . . . At that time, many of the important telephone lines went through Hungary and there were constant complaints that Hungary did not keep its lines in order. The method used to test a telephone line was to put an A.C. voltage on a line, beginning in Budapest, let the current go to the different capitals, and then feed it back to Budapest and compare the input with the output voltage for different frequencies. A single measure of the speech frequency range took more than 20 minutes. A few minutes after the measurement was completed, the lines were apt to be out of order again.

"I wanted to find a method that could complete the test in a second. The idea was that, when a musician tests his violin by plucking a string, he can tune it immediately. Theoretically, by plucking a telephone line it should be possible to obtain instantly all the data that are obtained by the cumbersome 20-minute test. Therefore, I transmitted a click through the line by switching in a small D.C. voltage and then listening and observing the returning signal. It turned out that the operator's switch always had some D.C. potential difference, and before long I was able to tell precisely in which city a disturbance of the lines had occurred just by listening to the clicks.

"Because of its simplicity, this click has attained primary importance in research on the inner ear."*

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*With acknowledgments to Theodore Sourkes: Nobel Prize Winners in Medicine and Physiology, 1966.

Who Follow a Gleam

Senor Manuel Garcia, The Laryngeal Mirror

"Remember that voice is the sound produced by the vibrations of the vocal cords. Remember that it is the air from the lungs which produces those vibrations. Unless you understand how your lungs are made, and your larynx with its precious vocal cords, you can never learn to sing—never!"

Thus were his pupils adjured by Senor Manuel Garcia, distinguished Spanish-born singer and vocal instructor, whose whole life and being were consecrated to the supernal art of singing but who, on a more prosaic plane, was avidly curious about the physiology of the voice. Just what specific action of the vocal cords produced high and low, loud and soft notes, Garcia wanted to know. How were the manifold voice registers correlated with the diverse cord formations and vibrations?

"During all the years of study and investigation of the problems of the voice-emission," Garcia said, "one wish was ever uppermost in my mind—'if only I could see the glottis!' "

Granted that whatever happened in the throat of a singer could be *heard* and *felt,* it could not be seen. The process was invisible! It availed Garcia nothing to peer down his own throat or the throats of his pupils. The tongue got in the way; besides no one could look around a curve.

Nevertheless, wanting to *see* became Garcia's magnificent obsession. He thought about it constantly.

One day while he was strolling in a Paris park and pondering on his fixation, a flash of sudden insight electrified him: why not use two mirrors to reverse the image? Hastening to the surgical-instrument maker Charrier's he bought a dental mirror and rushed home, where, seizing a hand mirror, he proceeded to experiment on himself. Holding the dental mirror in his throat and focusing the hand mirror so as to reflect the image, he saw illuminated by a sudden providential ray of bright sunlight—his own voice box! His admiring pupil and biographer Mackinlay describes his reaction:

"So dumfounded was he that he sat down aghast for several minutes. On recovering from his amazement he gazed intently for some time at the changes which were presented to his vision while the various tones were being emitted. From what he witnessed it was easy to conclude that his theory, attributing to the glottis alone the power of engendering sound, was confirmed, and thence it followed that the different positions taken by the larynx in the front of the throat had no action whatever in the formation of the sound. At last he tore himself away, and wrote a description of what he had seen."*

Six months later, on March 22, 1855, his paper, 'Physiological Observations on the Human Voice,' was submitted to the Royal Society of London.

But the medical world wasn't interested. After all, Garcia was just a singer—not a doctor! Who was *he* to be telling *them!* Maybe he could view his own throat, said they; but he was an exception—physiologically disciplined to manage such a maneuver. His dual-mirror contrivance was "just a toy!"

But it was that primitive, embryonic "toy" that was destined to become the laryngoscope: the instrument improved and perfected later by other medical Galahads following a gleam.

*Mackinlay, M. Sterling: Garcia the Centenarian, 1908.

Stromal Endometrioma Mimicking Acute Appendicitis

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We wish to record the story of a young mother who, while taking oral contraceptives, presented with symptoms and signs of acute appendicitis but turned out to have a rare uterine tumor—stromal endometrioma.

Case Report

A 29-year-old mother of three children came to the hospital on June 6, 1968, complaining of abdominal pain and loss of appetite. Both symptoms had started the day before when she sensed discomfort in the "pit of my stomach." After a few hours, she noticed pain in her right lower abdomen; however, she was not nauseated and did not vomit. For three years she had regularly ingested an anovulatory drug and could not recall the date of her last menstrual period.

When the physician first examined her, he elicited tenderness in the right lower quadrant but could not produce rebound tenderness. But as he bimanually palpated her uterus, he discovered an exquisitely tender spot on its posterior aspect. Because of this tenderness, he was unable to judge the size of the uterus. Her rectal temperature was 100.8, her white blood count 14,100 with 84 percent neutrophils, and her urinalysis normal. With this history, physical findings, and laboratory information, he diagnosed acute appendicitis.

But when he opened the abdomen through a right transverse incision he found no abnormality in the appendix; instead he saw a patch of mesosigmoid adhering to the back of the uterus. After separating this adhesion he came upon a dome-shaped protuberance where blood vessels converged: a small raised lesion, measuring less than two centimeters. He biopsied it, removed the appendix, examined other abdominal viscera, and, finding nothing else, closed his incision.

Pathologic Findings

When the pathologist read the biopsy, he observed fibrous tissue, hemosiderin pigment, and extravasated red cells. He suggested endometriosis as a possible diagnosis. But, because

of the absence of endometrial glands, he did not definitely commit himself to that diagnosis.

After the operation, the patient's abdominal pain ebbed. Six days after surgery she went home and resumed taking birth control pills. Three weeks later, on July 13, severe low abdominal pain recurred, and when it had persisted for 36 hours she consulted her physician, who detected diffuse lower abdominal tenderness and readmitted her to the hospital. Though she had no muscle rigidity and normal bowel sounds, this time he palpated a large tender posterior uterine mass. Again she was febrile (rectal temperature 100.0), again her white count was up (15,300 cells per cubic millimeter), and again her differential count showed a preponderance of neutrophils (79 percent). Adenomyosis* was suspected but thought to be an unlikely cause of her symptoms because she was taking anovulatory drugs. However, permission for a hysterectomy was obtained.

Two days later, the surgeons incised her abdomen through a suprapubic approach. Arising from the posterior uterus, they sighted a globular, rubbery mass in the same spot they had biopsied three weeks before. It had unquestionably enlarged since the previous operation. They enucleated it, resected the right fallopian tube which was fused to it by adhesions, and sewed up the hole in the uterine wall. The tumor measured 7 by 5 by 5 cm. and weighed 85 grams; grossly and microscopically it had the characteristics of a stromal endometrioma (Figures 1 and 2). The patient left the hospital 11 days later, stopped her oral contraceptives, and has been well since.

*See Test Your Word Score, Page 175.



Fig. 1—Low-power view of stromal nodule showing islands of stromal cells in fibrous matrix.

Discussion

Stromal Endometrioma

What is a stromal endometrioma? We regard it as a rare tumor of the wall of the uterus formed by endometrial stromal cells that overgrow: a straightforward answer, but an oversimplified one. Students of this condition apply an astonishing number of names to it—stromatosis, fibromatosis, endolymphatic stromal myosis, stromal adenomyosis, stromal nodule, stromal sarcoma, endometrial sarcoma, and hemangiopericytoma. Some feel these names describe different stages of the same lesion; others say they represent different lesions with different prognoses. But the confused name-calling represents more than histological hoopla; it reflects lack of unanimity as to the tumor's nature and uncertainty regarding its malignancy.

We think our patient's lesion was benign. True, we have only an 18-month follow-up. But the mass shelled out easily, had well-defined margins, did not invade vessels or lymphatics, and was free of mitoses. Norris and Taylor, who have the largest series in print with 53 cases, say that the number of mitoses and the presence of sharp margins are crucial prognostic points.[1] In their 16 patients who had non-infiltrating lesions, no tumor recurred after hysterectomy; and in 20 patients with fewer than 10 mitoses per 10 high-powered fields, the actuarian 10-year survival was 100 percent.

But stromal tumors are not always so innocent. Indeed, if they infiltrate into adjacent myometrium or push their way into lymphatics or vessels, about half the patients will die of metastatic disease.

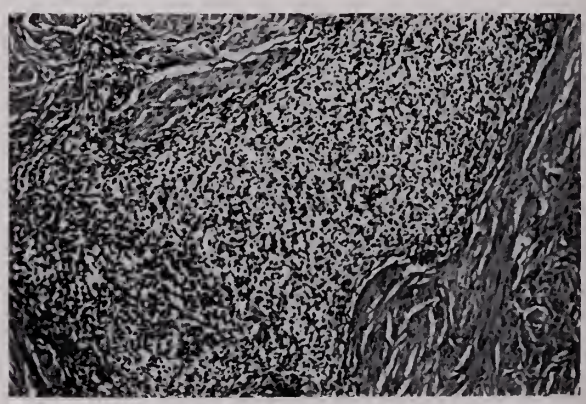


Fig. 2—High-power view of stromal cells showing well-differentiated nature of tumor.

Malignant Potential

So much for malignant potential. Now a few clinical points. The lesion is rare. Although Norris and Taylor collected 53 cases in 1966, another group of authors, writing in 1956, could cull only 94 from the world literature.[2] Stromal endometrioma tends to occur in middle-aged women (mean age about 45), and about one in four is postmenopausal.[1] Patients may bleed abnormally from the uterus, have severe pelvic or abdominal pain, experience a fullness in the pelvis, or actually feel a mass. This tumor grows independently of estrogenic hormones. Anovulatory drugs, which suppress the glandular elements of endometriosis, fail to suppress the growth of a stromal endometrioma.

Etiology

A final question. Did oral contraceptives cause our patient's tumor to grow faster? Certainly something stimulated it to expand rapidly in the three weeks between her operations. Nevertheless, our answer is: probably not. Anovulatory oral contraceptive agents have been casually blamed for causing many things; we do not wish to add to the list.

Still we ought to say that progestational agents cause endometrial stromal cells to swell (while endometrial glands shrink), giving the endometrium a decidual appearance, and that the drugs can produce "atypical" leiomyomas. Fechner, a pathologist at Methodist Hospital in Houston, recently reported five patients in whom oral contraceptives induced bizarre big nuclei, myometrial hypertrophy, or myometrial nodules.[3] All of these lesions were benign, and none of the changes resembled what we saw in our patient.

Reprints: 1224 Metropolitan Medical Center, Minneapolis.

Summary

A 29-year-old woman developed symptoms suggesting appendicitis. At operation we found a normal appendix and a slight bulge of the back side of the uterus with mesentery adhering to it. This resembled endometriosis.

Three weeks later the symptoms reappeared. The patient had resumed taking oral contraceptives after the operation, as had been her practice for three years. At reexploration of the abdomen, we enucleated a 7 x 5 x 5 cm stromal endometrioma from the uterus. The patient has been well since.

Stromal endometrioma is a rare mesenchymal tumor of the uterus that probably represents an overgrowth of endometrial stroma; it is painful and may be malignant, and its growth is thought to be independent of endogenous ovarian hormones. Although our patient was taking anovulatory drugs while the tumor was growing rapidly, we believe this to be a coincidence.

References

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Health

If an executive hasn't enough sense to take care of his own health, he hasn't enough sense to supervise other people, commented the head of a large Midwestern company. Recent survey of five hundred apparently healthy business leaders showed 41% suffered from ailments of which they were unaware; 71% had some physical abnormality; 52% were in need of immediate treatment; 11% "knew something was wrong" but "didn't have time" to seek medical advice.—Newsweek.

Tell the truth, and so puzzle and confound your adversaries.—Henry Wotton

Psychedelirium Tremens

Remember when *HIPPIE*—meant big in the hips,
And a *TRIP* involved travel—in cars, planes and ships?

When *POT* was a vessel—for cooking things in,
And *HOOKED* was what Grandmother's—rug might have been?

When *FIX* was a verb—that meant mend or repair,
And *BE-IN* meant simply—existing somewhere?

When *NEAT* meant well organized—tidy and clean,
And *GRASS* was a ground cover—normally green?

When lights and not people—were *SWITCHED ON* and *OFF*?
And the *PILL* might have been what you took for a cough?

When *CAMP* meant to quarter—outdoors in a tent,
And *POP* was what—the weasel went?

When *GROOVY* meant furrowed—with channels and hollows,
And *BIRDS* were winged creatures—like robins and swallows?

When *FUZZ* was a substance—that's fluffy like lint,
And *BREAD* came from bakeries—not from the mint?

When *SQUARE* meant a 90-degree—angled form,
And *COOL* was a temperature—not quite warm?

When *ROLL* meant a bun—and *ROCK* was a stone,
And *HANG-UP* was something—you did to a phone?

When *CHICKEN* meant poultry—and *BAG* meant a sack?
And *JUNK*—trashy castoffs and old bric-a-brac?

When *JAM* was preserves—that you spread on your bread,
And *CRAZY* meant balmy—not right in the head?

When *CAT* was a feline—a kitten grown up,
And *TEA* was a liquid—you drank from a cup?

When *SWINGER* was someone—who swang in a swing,
And *PAD* was a soft—sort of cushiony thing?

When *WAY OUT* meant distant—and far, far away,
And a man couldn't sue you—for calling him *GAY*?

When *DIG* meant to shovel—and spade in the dirt,
And *PUT ON* was what—you would do with a shirt?

When *TOUGH* described meat—too unyielding to chew,
And *MAKING A SCENE*—was a rude thing to do?

Words once so sensible—sober and serious
Are making the *FREAK SCENE—PSYCHEDELIRIOUS.*

It's *GROOVY, MAN, GROOVY*—but English it's not,
Methinks that the language—has gone straight to *POT.**

---

*Heard over Channel 2, KTCA, on a drug control series of telecasts.

Reduction Mammoplasty

CARL O. RICE, M.D.
Minneapolis, Minnesota

THE WEIGHT AND redundancy of a disproportionately large or hypertrophied breast may cause discomfort. Under these circumstances, a reduction in the size of the breasts by surgery may be indicated. Plastic restoration of an enlarged breast is also indicated in a male who has developed gynecomastia* which does not disappear in late puberty, and it is done solely for the purpose of removing the female contour. In this instance the adenomammectomy is more complete as there is no desire to retain the contour of the bosom.

Technique

In reducing the size of a hypertrophied breast, the important consideration is restoration of the contour to acceptable proportions as well as reducing uncomfortable weight. To accomplish this, meticulous technique is of utmost importance.

Incision

The incision should be made in the mammary thoracic fold (Figure 1) and should extend from the costosternal border to the serratus muscles laterally; in depth it extends to the areolar plane of tissue lying between the pectoral fascia and the breast substance. The surgeon must not make the mistake of placing the incision at a higher level than the mammary thoracic fold as this will distort the eventual contour.

The Adenomammectomy

The breast is dissected upward in the plane of the areolar tissue superficial to the pectoral fascia until the upper limits of the breast substance have been passed. This portion of the dissection can be done with the endotherm knife to minimize bleeding. The breast substance is then everted with the fingers of the left hand, and a subtotal adenomammectomy is done as previously described,† removing the breast sub-

*See Test Your Word Score, Page 175.
†Minnesota Med. 51:1325, 1968.



Fig. 1—Mammary thoracic fold incision. Note redundant right breast.

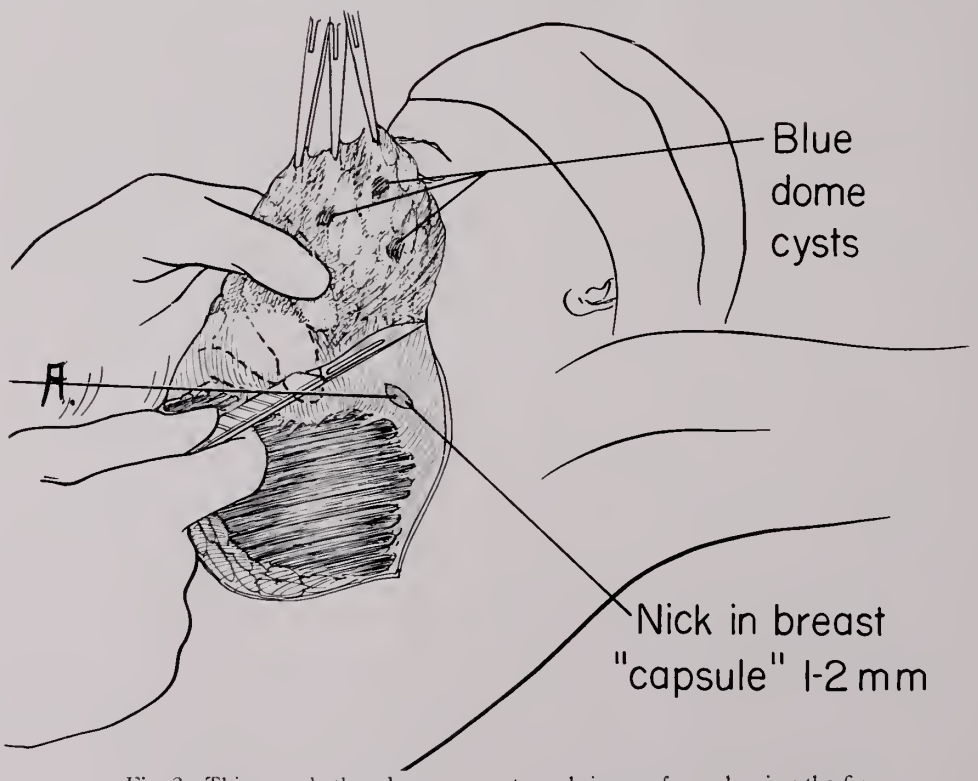


Fig. 2—This reveals the adenomammectomy being performed, using the fingers of the left hand to evert the breast substance during the dissection.

stance from the subcutaneous tissue but being meticulous to leave a layer of "breast capsule" (Figure 2 and 3). The endotherm knife is not used at this point lest the cauterizing blade inadvertently burn through to the underlying skin. In dissecting away the breast substance it is important not to enter the subcutaneous fat, for to do so causes scar tissue to grow into the skin, producing a puckering deformity. The criterion for determining the thickness of the remaining breast substance depends upon the desired size of the breast. Experience has taught that this depth of breast substance should not exceed 1 centimeter; often less. If the breast substance is occupied with fibrocystic disease, then the removal of breast substance must be more extensive than when there is no involvement.

Controlling the Bleeding

Meticulous hemostasis must be carried out, using pinpoint coagulation with the endotherm until the raw surface of the breast tissue and the opposing pectoral fascia are absolutely dry. The use of suture material is infinitely too time-consuming and results in more exudative reaction than pinpoint coagulation.

Reducing the Redundancy

After the adenomammectomy has been done, and the hemostasis of the raw breast surface and opposing pectoral fascia is complete, an approximation of the skin edges to one another will reveal an unwanted redundancy (Figure 4A). To reduce this redundancy, a crescent-shaped portion of skin and subcutaneous fat is removed from the chest wall beginning at the lower edge of the mammary thoracic fold incision and extending distally (Figure 5). The casual operator might be inclined to sacrifice the skin from the undersurface of the redundant breast. This must not be done, however, for to do so and then suture the skin edges to one another would merely place the nipple on the under surface of the breast, pointing toward the chest wall which, though reducing the redundancy, would be an unsightly distortion of the nipple's position (Figure 6).

After removing the crescent-shaped portion of skin and subcutaneous tissue, the skin edges are approximated, thereby placing the skin of the undersurface of the redundant breast on the chest wall. This position takes advantage of the redundant skin to close the elliptical defect. The skin will then lie flat on the chest wall (Figures 4-B and 6-A, B and C) and can be held in that position by a broad brassiere strap dressing.

The extent of the breast redundancy rather than the extent of the breast hypertrophy is a better criterion for the amount of skin to be removed: the greater the redundancy the greater the width of the removed crescent of skin.

Negative Suction

Before the skin edges are completely closed one or two large catheters are placed under the breast flap and brought out through an airtight stab wound below the site of the incision. A #90 polyethylene tube is placed into the lumen of the suction tube and brought out at the opposite end of the incision to serve as an air vent in order to keep the tube constantly open. After the wound is closed the tubes are attached to negative suction which is maintained for 72

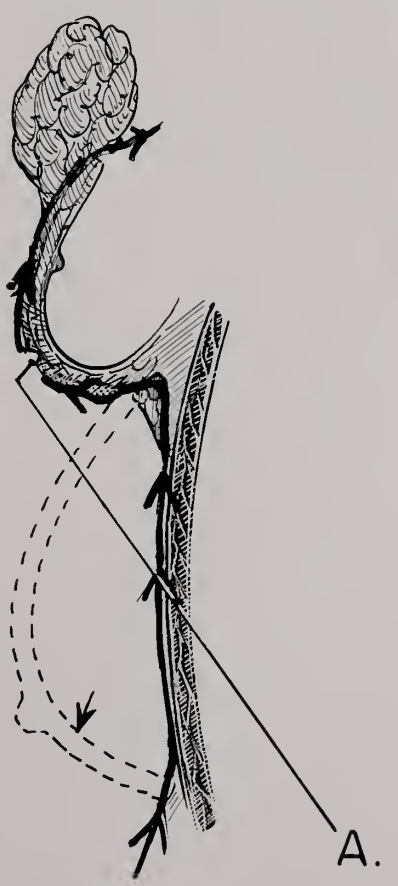


Fig. 3—This shows the line of dissection from the pectoral fascia and along the everted contour of the breast flap.

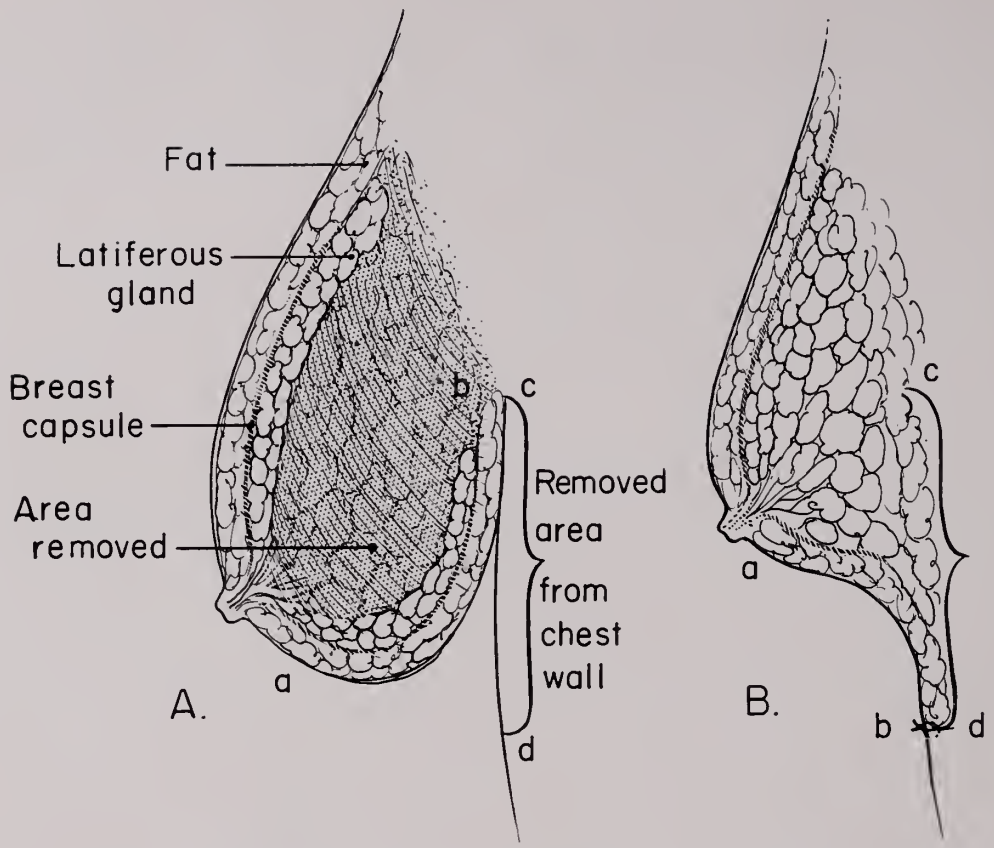


Fig. 4 (A)—This shows the redundant hypertrophy breast. (c to d) indicates the width of the elliptical flap removed from the chest wall as indicated in Fig. 5. (B) reveals that a to b represents that the redundant skin from the under-surface of the breast has been used as a "sliding graft" of sorts to close the elliptical defect of removed tissue c to d shown in Figure 5.



Fig. 5—The elliptical area of excision removed from the chest wall.

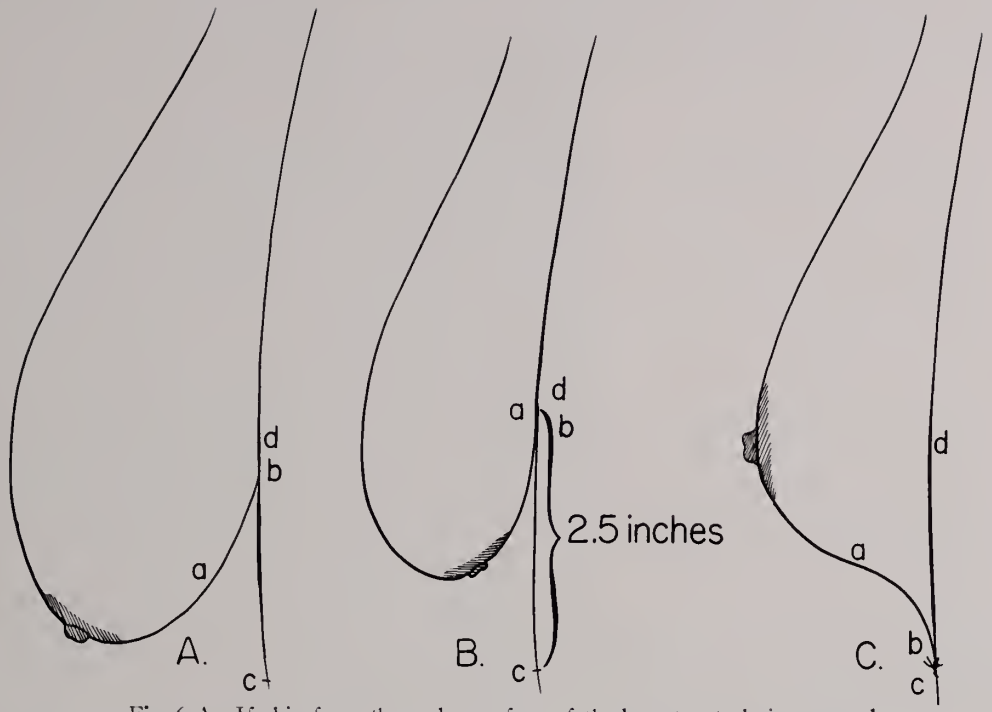


Fig. 6-A—If skin from the under surface of the breast, a to b, is removed, to reduce the redundancy, the nipple is turned inward as in B. When the elliptical area is removed from the chest wall, b to c, the redundant breast is used to close the defect, resulting in contour C.

hours. This suction under the breast flap prevents the accumulation of exudate and allows the breast tissue to adhere to the opposing pectoral fascia.

Postoperative Care

By positioning the patient in the almost flat supine attitude postoperatively rather than in the semi-upright position, the previously redundant breast can now be made to lie on the chest wall in a more normal position than was possible for the hypertrophied or redundant breast. In this position the cut-under surface of the breast tissue and the opposing surface of the pectoral fascia become adherent to one another in a position of repose, at a higher level than when the breast is allowed to hang at its maximum redundance. This semi-supine position is maintained for 72 hours. Over this period of healing, cells will proliferate enough to hold the breast at a higher level.

That portion of the skin and subcutaneous tissue placed on the chest wall from which the crescent of skin has been removed, much after the fashion of a sliding graft, must be held firmly onto the chest wall for 10 days with a broad strap of adhesive, thus eliminating the possibility of fluid accumulating under the breast flap, as such accumulation will float the tissue from its desired position.

No strapping or adhesive is allowed to pass across the contour portion of the breast in any area, as this would produce a palpable cleft at the point of pressure.

Conclusions

Adenomammectomy and plastic repair for massive hypertrophy or long redundancy of the breast carry only the minor hazards and risks that are associated with adenomammectomy. The hazards of nipple transplantation are eliminated. The resulting contour of the breast has been satisfactory in most of the patients in whom this procedure has been done.

Adenomammectomy and implantation of a prosthesis have not been done to enlarge a small breast or to provide contour for the breast.

If ignorance is bliss, an intelligence test is certainly a waste of time.—Herbert Prochnow

Medico-Legal

Donald G. Hagman, Professor of Law at the University of California, published in the July issue of the Journal of Forensic Sciences an article on the patient's right to medical records. It was based in part on responses to a questionnaire which the author sent to over 200 doctors in California and over 150 doctors in Minnesota. The answers to the questionnaire indicate that Minnesota physicians, by a vote of 2 to 1, believe that, in most situations, a patient has no right to see medical records concerning himself.

Mr. Hagman's summary of the medical view is "that patient medical records and the information on the records belong to the doctors or hospitals who prepare the records. Information from the records will be made available to others, particularly others in the medical profession, if the patient consents; but the patient or his representative is hardly ever entitled to have the records for his personal use, and he is not entitled to a copy or to information from it."

Mr. Hagman states that a medical record which contains evidence relevant to a lawsuit can almost always be obtained and that the medical profession refuses to believe that this is the law. He argues that medicine should change its views with respect to this matter so as to coincide with the legal view.

Jule M. Hannaford, Attorney
Minneapolis, Minnesota

Miracles of Surgery

A patient of the Spanish surgeon Francisco Arceo was a stone-mason struck on the head by a stone that fell from a sling while he was building a tower. The blow split the sagittal commissure, causing bleeding from the eyes and nose; the head and neck were swollen and black, and the man lay for three days as if dead. When the swellings subsided the physician and his assistant removed the bone fragments which had been pressing on the brain. On the third day the patient began to speak, although wandering in his mind; in two months his vision returned, and in two months more his squint was cured. When he rose from his bed he could not walk properly, but this was eventually corrected by the help of God.*

*The Patient's Progress by Felix Mart-Ibanez, 1962.

Editor's Note: Well, that was a remarkable recovery from a brain injury, but I expect that his inability to walk after having been in bed for two months was due to the long confinement. Early ambulation might have worked wonders.

Health

When I pointed out the folly of a male shop assistant coughing and sneezing near an exposed keg of butter without using a handkerchief, the young lady serving me replied innocently "Oh, it isn't butter, it's margarine!"—Letter to Sunday Dispatch (London).

Be ashamed to die until you have gained some victory toward humanity.—Mason.



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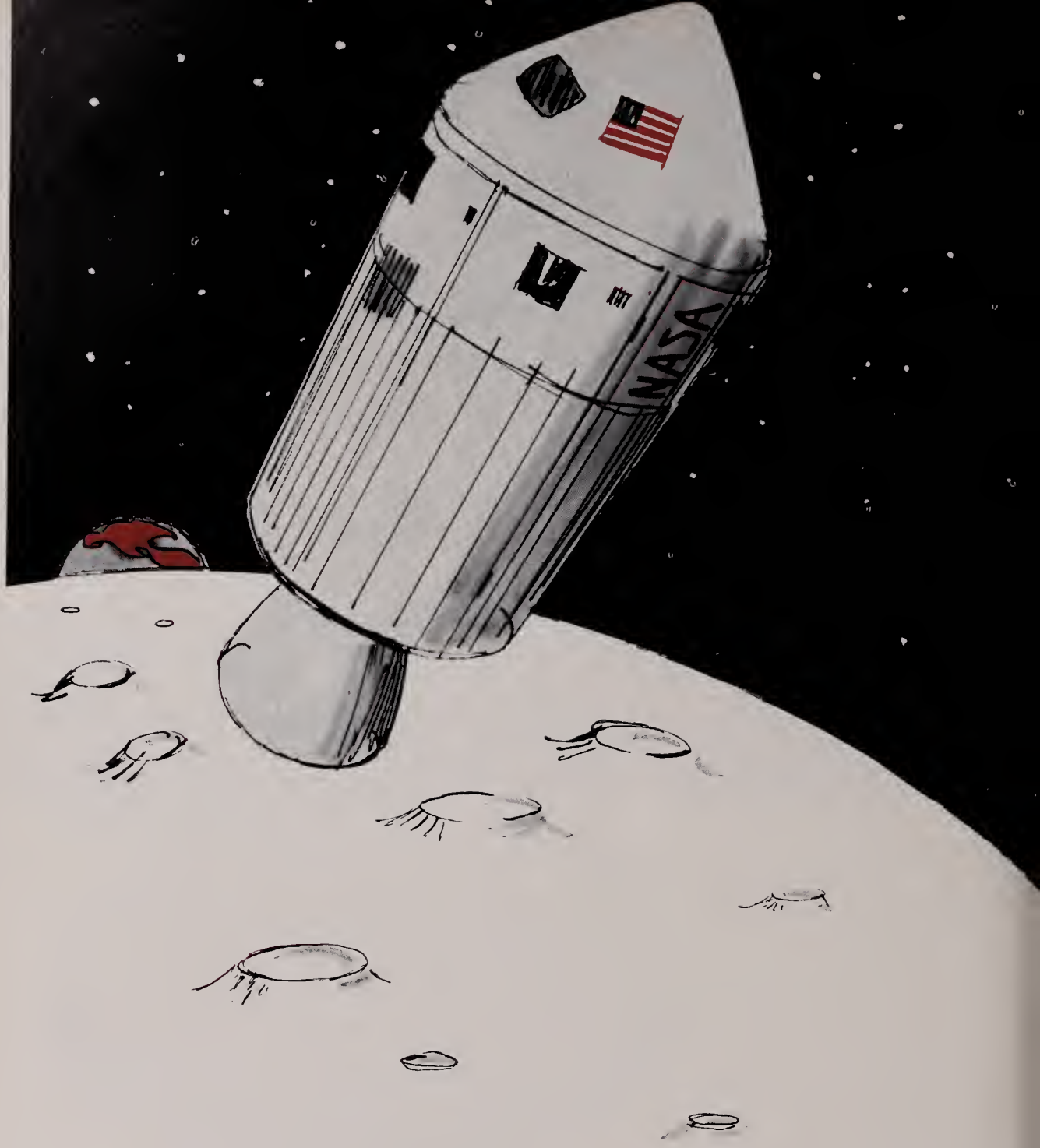
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Editorials

The Meaning of Medical Centers

THE TERM "medical center" may mean different things to different people.

To television viewers, it may mean a prime time drama in which transplants take place routinely.

To ghetto residents it may mean a place to go for medical help when you don't have a doctor of your own.

To rural dwellers it may mean any hospital or clinic to which you trek when you need a big operation or a specialist to figure out what sort of rare disease you have.

To city or suburban folk it may mean an all-purpose, full-service medical convenience center where parking is easy, access to doctors' offices simple, and facilities new.

To independent practitioners, generalists and specialists alike, it may mean a threat to your freedoms—the freedom to practice where and how you please, the freedom to choose your patients and to have them choose you, the freedom to remain a towering individualist on the medical landscape, and the freedom to treat your patients exactly the way you think they ought to be treated.

To specialists who generalize and generalists who specialize, it may mean a place where you commingle with your fellows, a teaching hospital where you can stimulate and be stimulated, or simply a centralized institution where you can park, maintain an office, and be close to diagnostic, therapeutic, and operating room facilities.

To toilers in academic groves (or grooves) it may mean a broadly and deeply based university complex where knowledge increases in quantum jumps, but in narrower and deeper channels.

To government and social planners it may mean an acceptable device for channeling the energies of doctors, for educating medical personnel, for closing the gulf between research and application, for easing the shortage of "health manpower," and for organizing "health resources" into "health teams" so as to spell the end of Medicine as a "cottage industry."

To hospital administrators it may mean that hospitals have finally come of age as business organizations, that medical tasks will be entrusted to institutions organized for social good and run by managers, that hospitals will be built, designed, and run more efficiently, and that hospitals will be institutions where doctors can mesh minds, maximize knowledge, and center their practice.

To me and others who work and practice at a medical center, it means change. And change is occurring, right here in the River Cities. Today the Twin Cities and environs have thirty-nine short-term hospitals, and at least a third of them are contemplating change. Hospitals within shouting distance of each other are either completing, discussing, or in the process of merging, sharing services, building connecting tunnels, constructing common buildings, or erecting adjoining medical office buildings—all steps towards forming medical centers.

To St. Barnabas and the Swedish Hospitals, the farthest along in most of these steps, the term "medical center" means the Metropolitan



Owner Breaks Arm When Yacht Runs Agroun

Schuyler, Oct. 31. Harry Waters of Covesville incurred a fractured arm ... tially capsized. The fire depar had to rescue Waters by small Damage to the yacht is estima

Hasn't the skipper had enough excitement for one day?

For the patient who has been through an accident, the worry and anxiety following the mishap may actually heighten the perception of pain. This is why there's a classic ¼ grain *sedative* dose of phenobarbital in Phenaphen with Codeine—to take the nervous "edge" off, so the rest of the formula can control the pain more effectively.

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Medical Center. What is the Metropolitan Medical Center? As far as its physical plant: it's St. Barnabas and the Swedish Hospitals linked together by a connecting unit. Together the two hospitals have 710 beds. In the adjoining unit are 189 more (making a total of 899 beds for the center). These include 51 beds for psychiatric patients, 30 for rehabilitating patients, and 108 for extended care patients. Across the street from this skein of buildings, connected by a carpeted underpass, stands a gleaming new 100-suite medical office building.

Right now, each hospital has its own administrative staff. So does the connecting unit. Of course, being in the same center, these three sets of administrators overlap, cooperate, and interdigitate.

And what of the medical staff? As you can see from articles in this issue, they are a diverse, independent lot: practitioners and specialists, physicians with their own sets of ideas, participants in the affairs of the center. All told, St. Barnabas has 285 physicians on its staff, Swedish about 226 on theirs. Many physicians have privileges on both staffs. As yet, the staffs function separately, though they participate in certain coordinating committees. Together the two hospitals have a single medical education program for interns, residents, and staff members, and separate education programs for nurses and technologists in different fields.

What does the Metropolitan Medical Center mean? In time, the physicians who practice there, the patients who come there, and the people who work there will answer that question.

Richard L. Reece, M.D.
Minneapolis, Minnesota

Work is something that when we have it we wish we didn't; when we don't have it we wish we did, and the object of most of it is to be able not to do any some day.—Phoenix Flame

Arteriomesenteric Occlusion of the Duodenum

Occlusion of the third portion of the duodenum by the superior mesenteric artery has provoked considerable controversy in recent years. The article by S. K. Imes* stimulated further interest in this somewhat bizarre condition.

Patients suffering from this condition are often young, asthenic, lordotic,† and somewhat anxious females, often unmarried. Interestingly, middle-aged and elderly patients are almost never afflicted with this disorder. Any factor which supposedly decreases the angle between the superior mesenteric artery and aorta, such as visceroptosis, weight loss and hyperextension of the spine, can enhance duodenal compression.

The most characteristic symptoms are fullness after eating and epigastric pain, both of which are relieved by assuming the knee-elbow or prone position.[1]

The incidence of this entity is probably somewhat less common than previously believed; in fact, one author questions the existence of the disorder.[2] The diagnosis cannot be entertained without radiologic evidence. Many of the x-ray findings such as reversed peristalsis in the duodenal loop, and a sharp cut-off of the lumen of the transverse duodenum adjacent to the spine are repeatedly shown to be normal variations. The radiologist should make every attempt to rule out other causes for obstructive disease in this area such as bands, adhesions, internal hernias, intrinsic and extrinsic tumors, particularly pancreatic.

Functional dilatation of the duodenum secondary to ulcer disease, cholecystitis and pan-

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*Imes, S. K.: Vascular Compression of the Distal Duodenum-Clinical Symptoms. Minnesota Med. 52:1055, 1969.

†See Test Your Word Score, Page 175.

in cardiac edema

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spares the potassium

Before prescribing, see complete prescribing information in SK&F literature or *PDR*.

Contraindications: Pre-existing elevated serum potassium. Hypersensitivity to either component. Continued use in progressive renal or hepatic dysfunction or developing hyperkalemia.

Warnings: **Do not use dietary potassium supplements or potassium salts unless hypokalemia develops or dietary potassium intake is markedly impaired.** Enteric-coated potassium salts may cause small bowel stenosis with or without ulceration. Hyperkalemia (>5.4 mEq/L) has been reported, in 4% of patients under 60 years, in 12% of patients over 60 years, and in less than 8% of patients overall. Rarely, cases have been associated with cardiac irregularities. Accordingly, **check serum potassium and BUN during therapy, particularly in patients with suspected or confirmed renal or hepatic insufficiency (e.g., certain elderly or diabetics). If hyperkalemia develops, substitute a thiazide alone. If spironolactone is used concomitantly with 'Dyazide', check serum potassium frequently**—their combined use can cause potassium retention and sometimes hyperkalemia. Two deaths have been reported in patients on such combined therapy (in one, recommended dosage was exceeded; in the other, serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving Dyrenium (triamterene, SK&F). Rarely, leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with the thiazides. Watch for signs of impending coma in acutely ill cirrhotics. Thiazides are reported to cross the placental barrier and appear in breast milk; thus adverse reactions which have occurred in adults may occur in the fetus or newborn infant. Rarely, thrombocytopenia or pancreatitis has developed in newborn infants whose mothers had received thiazides during pregnancy. When used during pregnancy or in women who might bear children, weigh potential benefits against possible hazards to fetus.

Precautions: Do periodic serum electrolyte determinations. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in postsympathectomy patients. The following may occur: hyperuricemia and gout, reversible nitrogen retention, decreasing alkali reserve with possible metabolic acidosis, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), digitalis intoxication (in hypokalemia). Use cautiously in surgical patients. Adjust dose of antihypertensive agents given concomitantly.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis; rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting (may indicate electrolyte imbalance), diarrhea, constipation, other gastrointestinal disturbances. Rarely, necrotizing vasculitis, altered carbohydrate metabolism, hyperbilirubinemia, paresthesias, icterus, pancreatitis, and xanthopsia have occurred with thiazides alone.

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creatitis is probably much more common than mechanical disorders. A rare entity known as hereditary megaduodenum shows a marked dilatation of the duodenum in the absence of obvious obstruction.[3]

A relatively recent article[4] has emphasized the use of lateral abdominal aortograms and measuring the aortomesenteric artery angle. In normal patients this angle measures 45 to 65°; in "duodenal-ileus" patients the angle is reduced to 10 to 15°. Further investigative studies such as this may shed more light on this disorder; meanwhile, an open mind must be kept on the actual incidence and the contributing causes of the syndrome. In most cases, apparently, except for the rare patient with complete obstruction, medical treatment often combined with psychotherapy will be sufficient.

Frank E. Mork, Jr., M.D.
Minneapolis, Minnesota

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The Decay of Civilization?

"WERE YOU TO ask me the cause of China's mental, moral and physical degradation, there could be but one answer, Opium."[1]

This was the statement and conviction of an early 20th-century medical missionary to China. It raises the question, however: was opium addiction as much a cause as a result of China's decadence from the late eighteenth into the early twentieth century? The latter view is endorsed by another close observer.

"For the spread of opium, like so many other social evils, is not an isolated development, but is dependent on the general trend of society in any given age. . . . The worse the condition of society, the more eagerly do men long for some kind of oblivion. All human beings would like to forget the distressing times in which they live and it is only natural that to this end weak people reach out readily for narcotics."[2]

"Opium smoking is a vice peculiarly appealing to the Chinese temperament, which likes indulgences of an effortless kind."[3]

"Although hippies deny it, smoking 'joints' or 'reefers' of marijuana pave the way for greater dependence on drugs later on. Police statistics show that virtually all users of heroin —'h,' or 'horse'—began by using marijuana and progressed from there! From marijuana, the novice progresses to LSD; then to 'speed'—methadrine or dexedrine benzedrine; and then to hard narcotics such as heroin."[4]

This raises another question! Isn't the human temperament much the same East or West, now as in the past? What induces Americans to overindulge in liquor, drugs and recently the variety of hallucinogens, tranquilizers and amphetamines? May not our own culture be deteriorating in this latter half of the twentieth century and may we not be offering a latter-day historic parallel?

True, present-day Americans don't feel the need to escape from the same economic and social evils as the earlier Chinese, who barely survived under the direst poverty and exploitation —unmitigated from birth to death. But the symptoms of cultural deterioration don't have to be grinding physical poverty and inhuman economic exploitation. Other signs of the insidious syndrome can be psychological and spiritual: denial of bright hopes, desecration of high ideals, defeat of noble purposes. Is it possible that total disillusionment with a materialistic, fragmented, and corruptible society, especially during a war crisis, makes it mandatory that escape become a must to the sensitive soul?

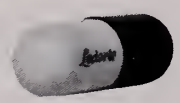
"Poverty as well as wars and social unrest are at present stimulating addiction, especially in the East. And it is obvious that the whole problem of opium and drugs is closely connected with the social upheavals which are now upsetting our restless world. In fact, terrible as this is, the problem of the licit, as well as the

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Precautions: Nonsusceptible organisms may overgrow; treat superinfection appropriately. Tetracycline may form a stable calcium complex in bone-forming tissue and may cause dental staining during tooth development (last half of pregnancy, neonatal period, infancy, early childhood).
Adverse Reactions: *Gastrointestinal*—anorexia, nausea, vomiting, diarrhea, stomatitis, glossitis, enterocolitis, pruritus ani. *Skin*—maculopapular and erythematous rashes; exfoliative dermatitis; photosensitivity; onycholysis, nail discoloration. *Kidney*—dose-related rise in BUN. *Hypersensitivity reactions*—urticaria, angioneurotic edema, anaphylaxis. *Intracranial*—bulging fontanels in young infants. *Teeth*—yellow-brown staining; enamel hypoplasia. *Blood*—anemia, thrombocytopenic purpura, neutropenia, eosinophilia. *Liver*—cholestasis at high dosage. Upon adverse reaction, stop medication and treat appropriately.

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illicit, drug traffic will find no solution until a lasting international and domestic social peace has been restored."[2]

By way of an early historic parallel we learn that during the decline of Greece and Rome the use of opium soared in those Mediterranean countries.

"Physicians and their patients had less constraint and self-control than they had when Graeco-Roman civilization was at its height. They needed more artificial stimuli, they could stand less pain. They seemed to think more of the present than of the future. Opium, which drugged the pain or the anxiety of the moment, was taken in greater quantities—the inevitable effects of the drug tomorrow or the next day were forgotten.

"Galen, the most fashionable and the most able physician in Rome in the second century, who had a habit of running away from the City and his patients whenever an epidemic broke out, gave opium freely to the effete, charming Romans who came to him for medical advice."[2]

"Hippies are victims of the same hypocrisy and double standards which they so volubly reject. They themselves are guilty of phoniness, shams, pretense and self-delusion. Hippiism has resulted from the sickness of society. It could never have arisen in the first place, and could never have gained such seemingly widespread popularity among hundreds of thousands, except for the fact that society is SICK!"[4]

Galen praised opium above all other drugs and his recommendation of it sounds like a twentieth century publicity campaign on behalf of some manufacturer of a new drug.

" 'Opium,' Galen wrote in the second century A.D., 'resists poison and venomous bites, cures inveterate headache, vertigo, deafness, epilepsy, apoplexy, dimness of sight, loss of voice, asthma, coughs of all kinds, spitting of blood, tightness of breath, colic, the iliac poison, jaundice, hardness of the spleen, stone, urinary complaints, fevers, dropsies, leprosies, the troubles to which women are subject, melancholy and all pestilences.'

"Many of Galen's weaker-minded patients eagerly took his advice, and reached out for opium whenever they had a slight pain. Large quantities of opium were consumed during this decadent age."[2]

"LSD is not a mind-awakening drug but a powerful poison which can derange the mind, scramble the brain, and kill! Using LSD is a chemical method of playing the age-old game of Russian roulette."[4]

"The fact that Galen, intellectually a most capable physician, had so little discrimination in his prescriptions, and completely forgot the moral aspects of the Hippocratic Oath, was symptomatic of the decay of the Graeco-Roman civilization."[2]

So, shall we indict the social order *per se* or those members of it who "want out?" Indeed, whether such repudiation of one's social heritage and rejection of its values and mores is justified or not—is not the issue! It can always be argued that the propensity to escape shows lack of moral stamina. True! But may not that very dearth also be a product of the manifest decay so inevitable in a culture whose scientific and technological advance has left its morality so far behind as to be almost anachronistic.*

"Millions of American youths, while not 'hippies' in the sense that they are portrayed here, are still very much in sympathy with much of the hippie 'philosophy.' In short, disillusionment with adult society; rejection by parents; resentments toward frightening world conditions all play a part in causing young people to 'drop out.' Put all this together with the seemingly exciting attractions of wild 'pop' and 'folk' music—the mystery of mind-expanding drugs; the euphoric sensations of marijuana and the lurid enticement of 'love' and sex—and you've got a powerfully potent psychological narcotic for otherwise disinterested teenagers."[4]

Is there a parallel? Is there an American-Chinese-Graeco-Roman parallel?

Our civilization will not decay, but let's get off our duff.*

Carl O. Rice, M.D.

*See Test Your Word Score, Page 175.

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Pharmacologically, papaverine acts on cardiac and smooth muscle[1,2] including the arterial musculature of cerebral[2] and coronary[3] vessels.

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Each capsule contains papaverine hydrochloride, 150 mg., in timed disintegration pellets for sustained release. Class M exempt drug. *Indications:* Relief of cerebral and peripheral ischemia associated with arterial spasm, and myocardial ischemia complicated by arrhythmias. *Side Effects:* Rarely nausea, abdominal distress, anorexia, constipation, malaise, drowsiness, vertigo, sweating, headache. *Contraindications:* Use with caution in patients with glaucoma. *Dosage:* 1 capsule every 12 hours. May be increased to 1 capsule every 8 hours.

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Selectivity in Lumbar Puncture

LUMBAR PUNCTURE and the study of cerebrospinal fluid, as is true of other diagnostic procedures, do contribute to the study and management of some patients. Procedures, however, should be considered secondary to the thoughtful use of the results of history-taking and physical examination. Judgment is required to decide which procedures to do and in what order, as well as whether the information to be gained justifies the known risks and, I might add, the expense to the patient. A valid test to be applied, as suggested by Long, Seljeskog, Chou, and French,* is whether the proper procedure can be dictated by the probable results. A stuporous patient with nuchal rigidity may have subarachnoid hemorrhage or bacterial meningitis; to treat him properly, the physician needs to know which.

Because neurologic or neurosurgical consultation is not available in many parts of the country, the physician may be faced with the problem of trying to gather as much information as he can in order to make his referrals to medical centers more selective. In addition to the potential risk to the patient who actually has a tumor in the head or in the spinal canal, the authors wisely point out the true but not generally known fact that recent spinal puncture makes pneumography and myelography more difficult to execute and interpret. I would submit, therefore, that, if he believes his patient may have a tumor, the physician who practices in an area without available neurologic consultation should telephone the neurologist or neurosurgeon to whom he might refer the case.

Many lumbar punctures are done to reassure the physician or his patient that the headache is *not* caused by brain tumor, and punctures done to obtain this type of information undoubtedly will continue. I would guess, however, that false reassurance would equal the extraordinarily low positive yield in such indications. In lumbar punctures and the stock market alike, "Be selective" seems the best advice.

Donald D. Layton, Jr., M.D.
Rochester, Minnesota

*Long, D. M., Seljeskog, E. L., Chou, Shelley N., and French, L. A.: Acute Neurological Deterioration Following Lumbar Puncture. Minnesota Med 52:247, 1969.

Test Your Word Score

Latitudinarian—*one indifferent to, opposed to, or deviating from strict interpretation of doctrine* (page 134).

Exegetical—*explanatory, expository* (page 134).

Hematinic—*a substance efficacious in increasing the hemoglobin content of the blood* (page 135).

Anisocytosis—*inequality of cell sizes, especially of red blood corpuscles* (page 136).

Hyperpiesis—*abnormally high pressure* (page 138).

Thrave—*a small bundle shaped like a sheaf* (page 142).

Pressor—*tending to increase blood pressure* (page 150).

Adenomyosis—*benign invasion of the endometrium into the uterine musculature, with diffuse overgrowth of the latter* (page 154).

Gynecomastia—*excessive development of the male mammary glands* (page 157).

Lordotic—*afflicted with spinal curvature* (page 169).

Anachronistic—*incongruous in point of time* (page 173).

Duff—*if you don't like the way things are—do something about it.*—Random House dictionary, unabridged (page 173).

Parabasal—*cytoplasmic* (page 187).

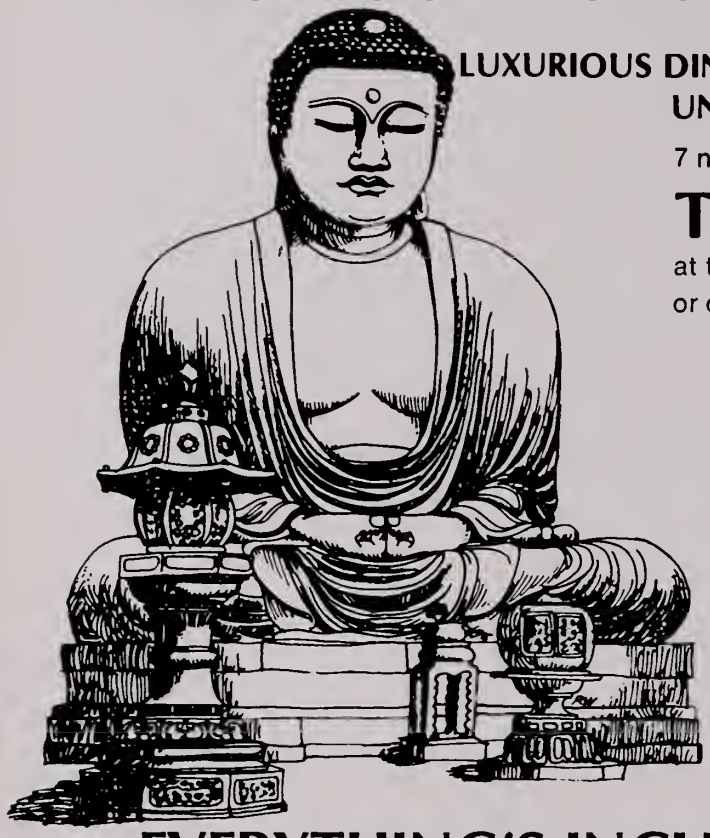
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You May Be Right

Dial Access Medical Library

CRITICAL APPRAISAL of the value and cost of the many innovative programs being instigated in the health care system is both justified and desirable. The Regional Medical Program was developed to catalyze changes designed to bring about improvements in the delivery of health care services. Our greatest challenge is objective evaluation of benefits and costs.

An initial evaluation indicates successful use of the Dial Access Library service in the first year of operation. The toll-free telephone medical information service provided current technical and treatment advice in abstract form to 1,236 physicians who placed 3,657 calls to the Library.

One fourth of Minnesota's practicing physicians used the service at least once during the year. In the eleven economic regions the percentage of general practitioners using the Library varied from 30% to 48%, and the percentage of specialists from 13% to 35%.

An 85% response to an evaluation questionnaire was obtained from a stratified random sample of physicians using the Library (N=441). Answers to the four questions were as follows:

(1) Check one or more reasons for using the Library: To improve knowledge about a specific topic—71%; To confirm treatment of an emergency case—25%; To obtain information about recent advances—47%; To test a new communication medium—33%; Pure curiosity—16%.

(2) Have you ever called because of a specific condition of a particular patient? Yes—66%. In the eleven regions the percentage varied from 52% to 100%.

(3) In which of the following ways has the system assisted you? Provided new ideas for improving patient management—40%; Provided useful reassurance—53%; Updated medical knowledge—58%; Of no or little assistance—10%.

(4) Which of the following directions should the Library now pursue? Continue present operation—78%; Provide service to other health care personnel—11%; Include tapes covering additional topics—44%; Provide manuscript of tape—29%; Discontinue the service—3%.

The average cost for the operation this year was $2.55 per call. The telephone bill represented 74% of the cost, or $1.88 per call.

Although not a panacea, it would seem that the program is worthy of expansion. Nurses, dentists and technologists would like to be included, and many suggestions have been received for additions.

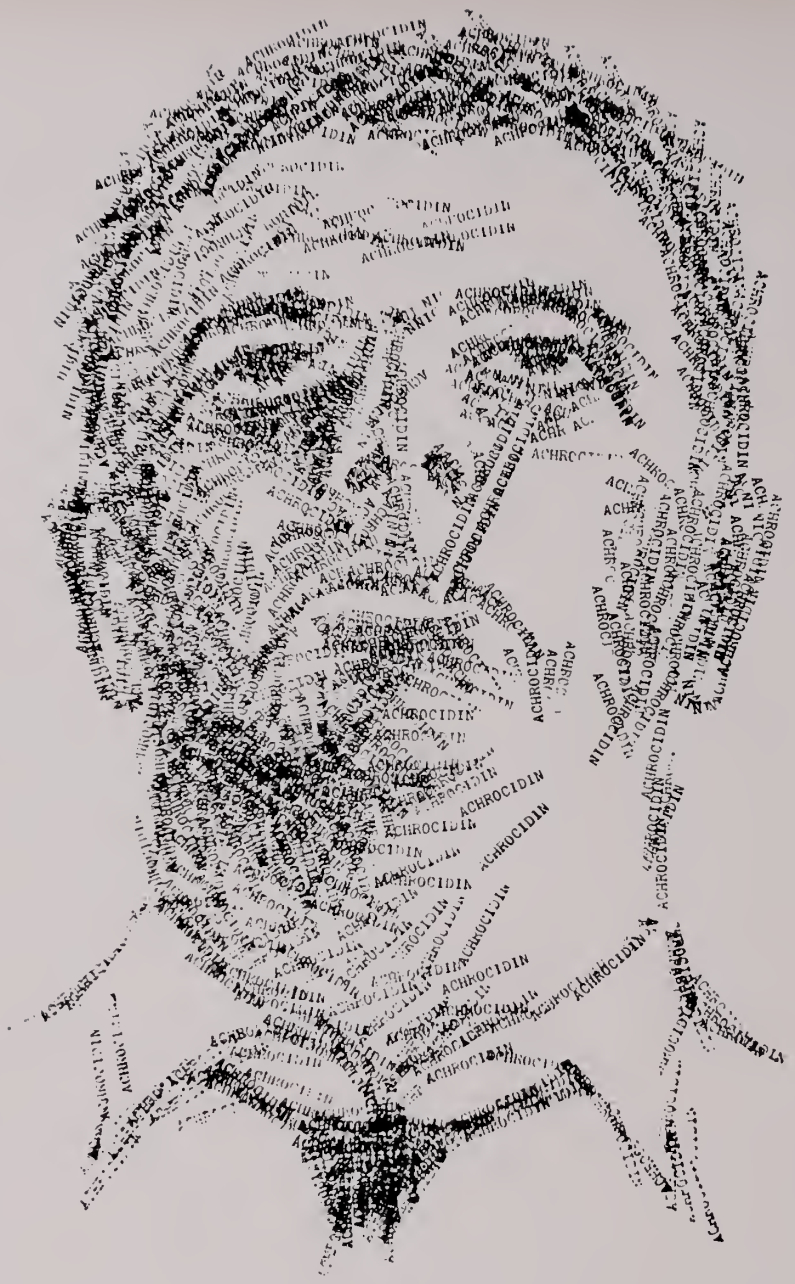
Other planned innovations by NRMP in Continuing Education include assistance for better telephone consultations, better library services, better educational programs in community hospitals and in medical centers, and improved uses of television.

Concomitant research in objective evaluation technology should progressively improve our ability to demonstrate cost benefits, cost effectiveness, and cost efficiency. Hopefully this technology will be comparatively applied to the older traditional methods also.

Winston R. Miller, M.D.
Program Director
Northlands Regional Medical Program, Inc.

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Contraindications: Hypersensitivity to any component.

Warning: In renal impairment, since liver toxicity is possible, lower doses are indicated; during prolonged therapy consider serum level determinations. Photodynamic reaction to sunlight may occur in hypersensitive persons. Photosensitive individuals should avoid exposure; discontinue treatment if skin discomfort occurs.

Precautions: Drowsiness, anorexia, slight gastric distress can occur. In excessive drowsiness, consider longer dosage intervals. Persons on full dosage should not operate vehicles. Nonsusceptible organisms may overgrow; treat superinfection appropriately. Treat beta-hemolytic streptococcal infections at least 10 days to help prevent rheumatic fever or acute glomerulonephritis. Tetracycline may form a stable calcium complex in bone-forming tissue and may cause dental staining during tooth development (last half of pregnancy, neonatal period, infancy, early childhood).

Adverse Reactions: *Gastrointestinal*—anorexia, nausea, vomiting, diarrhea, stomatitis, glossitis, enterocolitis, pruritus ani. *Skin*—maculopapular and erythematous rashes; exfoliati dermatitis; photosensitivity; onycholysis, n discoloration. *Kidney*—dose-related rise BUN. *Hypersensitivity reactions*—urticar angioneurotic edema, anaphylaxis. *Intracran* —bulging fontanels in young infants. *Teeth* yellow-brown staining; enamel hypoplasi *Blood*—anemia, thrombocytopenic purpur neutropenia, eosinophilia. *Liver*—cholestasis high dosage.

Upon adverse reaction, stop medication a treat appropriately.

The Editor's Soliloquy

Dial Access*

Words, phrases, proclamations, figures and headlines may have an uncanny disposition for deceiving the mind. Testimonials and statistics may be notorious in this regard.

In 1968 the Wisconsin Regional took over Dial Access and proudly announced having answered more than 13,000 calls from Wisconsin doctors endeavoring to obtain "better patient care under the new regional programs."* The Dial Access tape requires 5 or 6 minutes to detail the diagnosis, treatment, or prevention of a specific disease: a "canned consultation," as it were.

With approximately 4,000 doctors in the State of Wisconsin this averages about 15 minutes listening time "for continuing education" in the past two years: equivalent to 7½ minutes per year per doctor.

A similar evaluation by Northland Regional, Minnesota, revealed essentially the same average annual utilization per doctor. Minnesota's budget from the Federal government is one and a quarter million dollars; Wisconsin's is $985,000.

"Each region has a Citizen's Advisory Council composed of medical and non-medical community leaders. The Council determines what the health needs of its area are and must approve all programs before they receive Federal funds."*

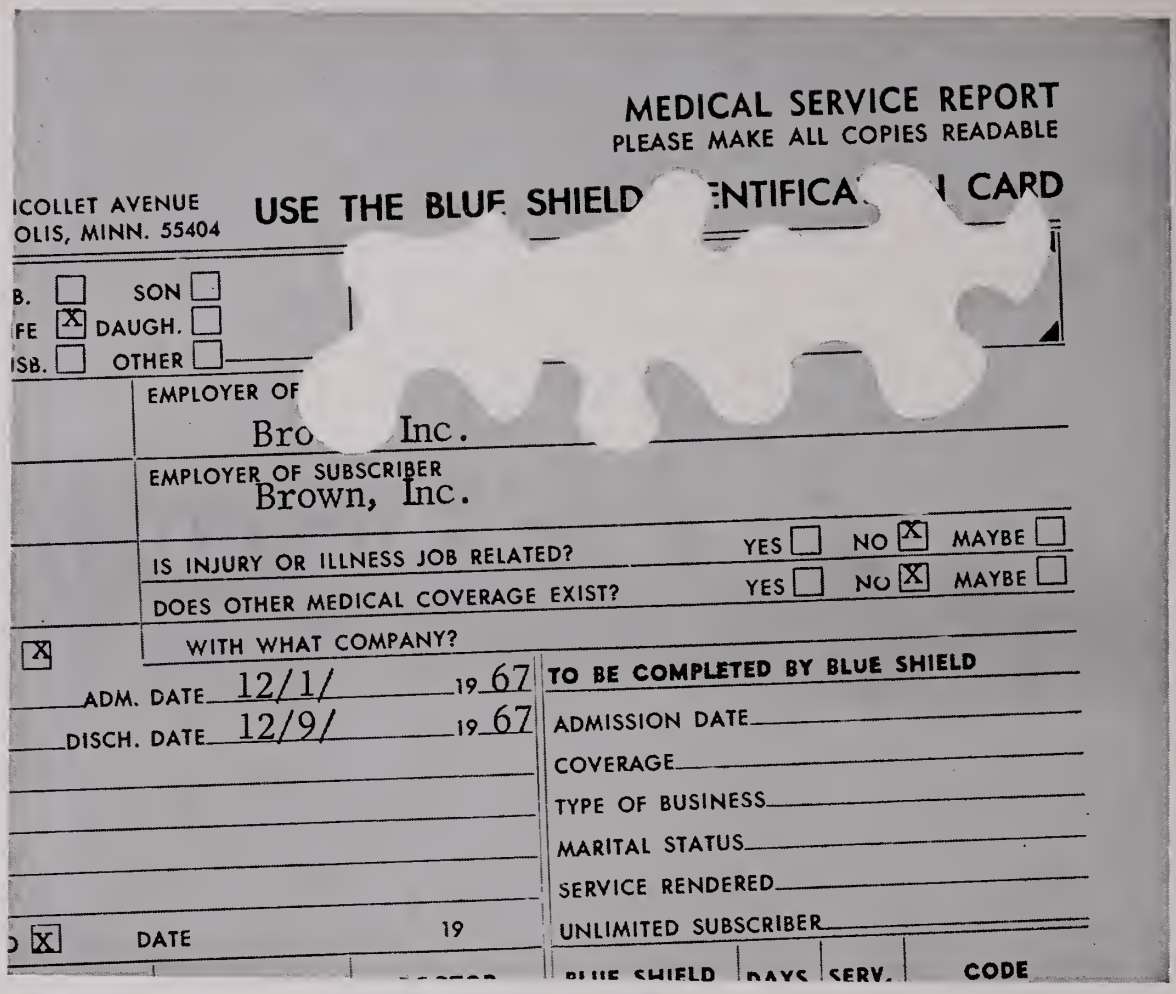
One doctor used the tapes for continuing education as a surrogate bedtime story. Another physician's testimonial in the Wisconsin Regional study* observed that his young patient's pulse rate had leaped on one occasion and that, after studying the x-rays, he had concluded that his patient was suffering heart failure. Whereupon he immediately had called the Dial Access library, listened to the brief recorded lecture, followed the recommendation, and—you guessed it—without Dial Access the outcome might not have been so happy!

This, in the regions where some of the most famous medical centers on this little earth of ours are located; where medicine has been and still is practiced on the highest scientific and ethical plane; where a live ear-to-ear consultation is available at the other end of the line any hour of the day or night, or an eyeball-to-eyeball consultation, within the hour!

*National Observer, December 29, 1969.

Carl O. Rice, M.D.

OLD DOC HESS SAYS: In the life of a doctor, "from portal to portal, there are unfortunately only 16 working hours in each day and so much to do in order to keep the balance for good outweighing the balance for evil."—C.O.R.



Missing Something ?

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Curbstone Consultation

Epidemic Hemorrhagic Fever

QUESTION: I have heard very little about epidemic hemorrhagic fever recently. Several years ago many of our soldiers in Korea were afflicted with this disease. Have there been any recent outbreaks among our troops stationed there? What is the etiologic agent in this condition, and has a specific therapy been developed against it?

ANSWER: Yes. There are about 10 to 12 cases of epidemic hemorrhagic fever in our troops stationed there each year. The etiologic agent is thought to be a virus. There is no specific therapy, but all cases respond to symptomatic treatment and there have been no fatalities in recent years. There are also no residual effects in those troops that have had the disease and return home.

QUESTION: Has this disease entity afflicted any of our troops in South Vietnam? If so, are we to anticipate finding the disease among our veterans returning from that war theatre? Are there any late manifestations that one should be alerted to among those who have contracted the disease in the past?

ANSWER: No. Epidemic hemorrhagic fever has not afflicted any of our troops in South Vietnam. Nor are there any late manifestations of the disease recorded in those patients that contracted the disease in Korea. Also in those patients in Korea that were treated there have been no relapses. The etiologic agent has not been isolated and there has been no vaccine developed.

Thomas A. Haedicke, M.D.
Montgomery, Alabama

War

Wars are always, and revolutions are nearly always, nasty, brutal, barbarous, stupid, sordid, and dreary. They are, while they last, the antithesis of civilization.

—Leonard Woolf

There is only one way to coast—downhill.—Canadian Business

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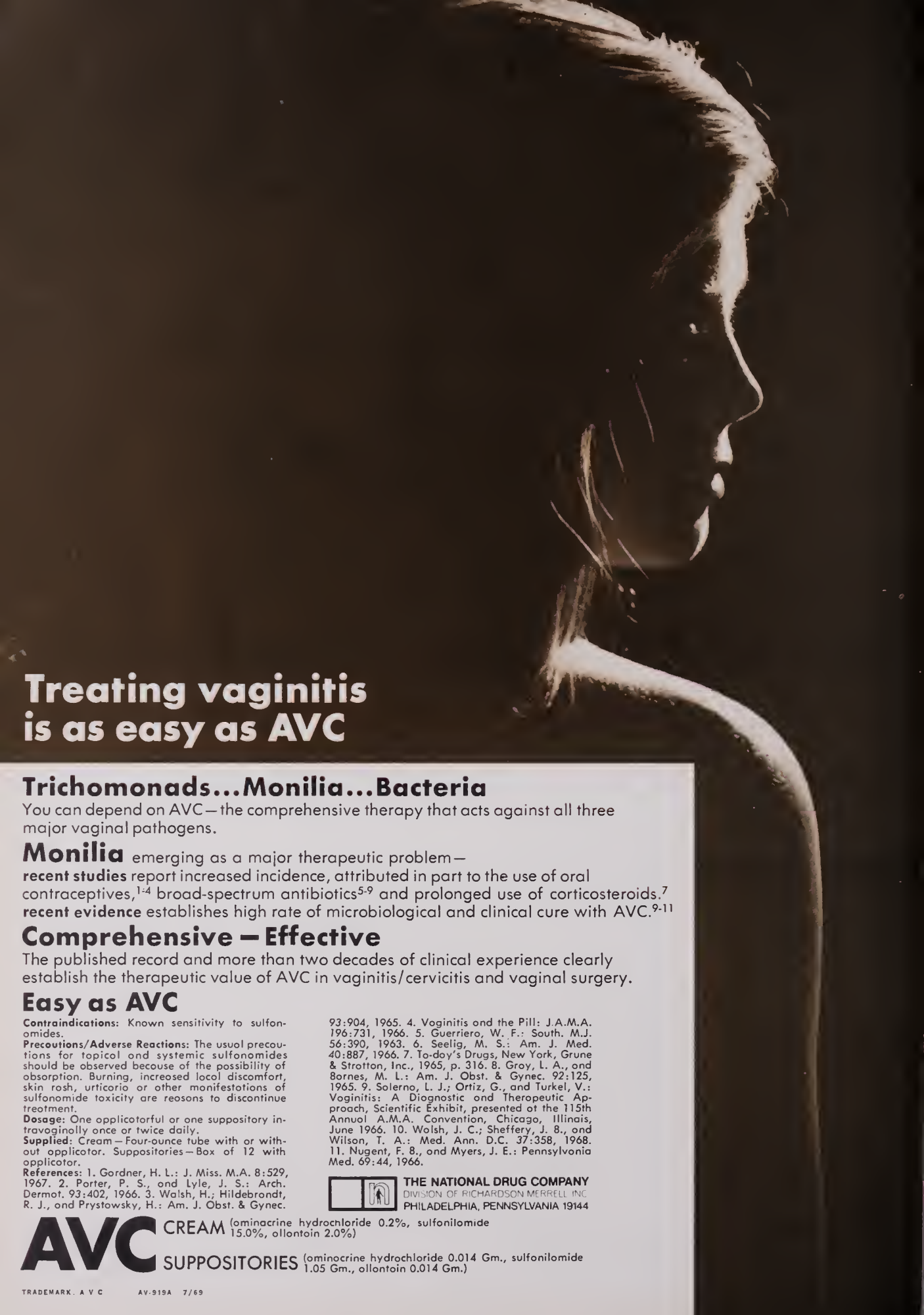
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Supplied: Cream—Four-ounce tube with or without opplicotor. Suppositories—Box of 12 with opplicotor.

References: 1. Gordner, H. L.: J. Miss. M.A. 8:529, 1967. 2. Porter, P. S., ond Lyle, J. S.: Arch. Dermot. 93:402, 1966. 3. Walsh, H.; Hildebrondt, R. J., ond Prystowsky, H.: Am. J. Obst. & Gynec. 93:904, 1965. 4. Voginitis ond the Pill: J.A.M.A. 196:731, 1966. 5. Guerriero, W. F.: South. M.J. 56:390, 1963. 6. Seelig, M. S.: Am. J. Med. 40:887, 1966. 7. To-doy's Drugs, New York, Grune & Stratton, Inc., 1965, p. 316. 8. Groy, L. A., ond Bornes, M. L.: Am. J. Obst. & Gynec. 92:125, 1965. 9. Solerno, L. J.; Ortiz, G., and Turkel, V.: Voginitis: A Diognostic ond Theropeutic Approach, Scientific Exhibit, presented ot the 115th Annuol A.M.A. Convention, Chicago, Illinois, June 1966. 10. Wolsh, J. C.; Sheffery, J. B., ond Wilson, T. A.: Med. Ann. D.C. 37:358, 1968. 11. Nugent, F. B., ond Myers, J. E.: Pennsylvonio Med. 69:44, 1966.

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The Viewing Box

Abdominal Pain and Vomiting in a Post-Coronary Patient

The patient is a 48-year-old white male who entered the hospital with complaints of upper abdominal pain and intermittent vomiting of six hours' duration. Three days prior to admission, spontaneous ecchymosis of the right ankle and left forearm developed. The patient had been on anticoagulants for approximately one month prior to his present illness following an acute posterior wall myocardial infarction.

An upper gastrointestinal series was performed, which demonstrated a persistent constricted area in the proximal jejunum about 6 centimeters in length (arrow Figure 1). Fluoroscopic and spot film (Figure 2) evaluation of this area reveals slight but incomplete expansion of the bowel. An intact mucosal pattern is seen, but the mucosal folds have the appearance of being swollen or edematous. The normal feathery appearance of the mucosa is absent and the jejunal margins show "spikes" of varying height.

What is your diagnosis? (See next page.)



Figure 1



Figure 2

Diagnosis: Intramural hematoma of small intestine secondary to anticoagulant therapy.

The radiographic findings together with laboratory evidence of abnormally prolonged prothrombin time and strongly positive stools for occult blood helped make the presumptive diagnosis of intramural small bowel hematoma. This was further substantiated when the patient's symptoms improved on conservative medical management and a repeat upper gastrointestinal series two weeks later was completely normal.

Intramural small bowel hemorrhage, while an uncommon clinical entity, is being recognized with increasing frequency as a complication of bleeding disorders and anticoagulation therapy. The clinical presentation may be quite varied and the diagnosis is often unsuspected. Because this condition can simulate an acute surgical emergency, unnecessary operations may be performed. Recognition of this entity, therefore, may have a significant bearing on treatment and prognosis in affected patients.

Numerous causes for intramural small bowel hemorrhage have been documented, including blunt abdominal trauma, anticoagulant therapy, Henoch-Schönlein purpura, hemophilia, leukemia, idiopathic thrombocytopenia purpura, liver disease, pancreatitis and uremia. Blunt abdominal trauma is the most frequent cause, with the duodenum and ileocecal region the most common sites of involvement. Anticoagulation therapy is the most frequent cause of non-traumatic small bowel hemorrhage, with the jejunum being the most common site of occurrence. Recognition of this entity as a complication of anticoagulation therapy is important, since conservative medical management has been shown to result in complete resolution.

The clinical manifestations relate to the degree of bleeding and amount of bowel obstruction present. The symptoms may vary from mild upper abdominal distress with nausea, emesis and a non-specific pain pattern to a picture of acute intestinal obstruction.

Radiographic manifestations are usually absent or non-specific on the plain supine abdominal film. Barium or other contrast studies demonstrate an infiltrative pattern in the involved bowel segment, which may be localized or diffuse, anywhere in the large or small intestine. In the upper small bowel, the normal feathery mucosal pattern is replaced by thickened mucosal folds with sharp delineation of their margins giving a parallel arrangement which has been described as "a stack of coins" or "picket fence" appearance. Another well recognized pattern is that of a "coiled spring," a term usually used to refer to small intestinal intussusception. These features are secondary to diffuse dissection of blood through the intestinal wall. Localized submucosal hematoma may also produce intramural filling defects in the contrast column referred to as "thumbprinting."

Although these radiographic appearances are characteristic of intestinal intramural hematoma, they are not absolutely diagnostic of this condition. Mesenteric vascular occlusion with acute segmental or diffuse intestinal infarction may produce an x-ray and clinical picture similar to intramural hemorrhage. Infiltrative lesions of the small bowel including amyloidosis, Whipple's disease, intestinal lymphangiectasia and small bowel lymphoma may also produce a similar radiographic appearance. However, these conditions can usually be differentiated by other clinical and laboratory methods.

William J. Boardman, M.D.*
Minneapolis, Minnesota

*Department of Radiology, Swedish Hospital.

Laboratory Letter

Superficial Cells

LET'S SAY you are caring for a 46-year-old housewife who stopped menstruating six months ago. She is edgy, has lost her sex drive, is concerned about aging, and complains of hot flashes, sweating, and nervousness.

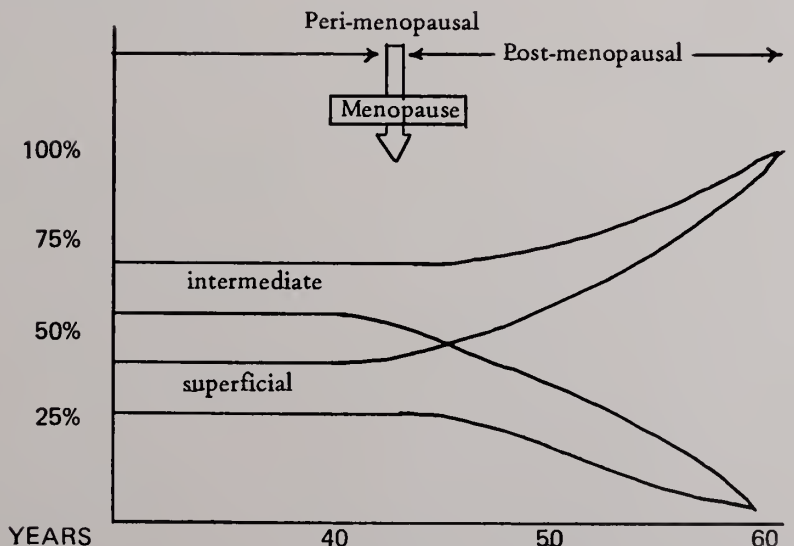
To ease her symptoms, you decide to start her on daily stilbesterol. You want to give her just enough hormone to relieve her distress, but not enough to cause endometrial bleeding. So you continue to see her in your office, but you try to titrate her estrogen dose against her symptoms, hoping to achieve the right hormonal balance.

If you knew the Maturation Index, you could probably be more precise in this therapeutic balancing act. How? By aiming for 15 to 30 percent superficial cells on the Maturation Index. If the percent falls below 15, increase the estrogen dose. If the percent exceeds 30, lighten the dose.

So much for how you regulate the dose. Now for the procedure itself and what it reflects. The Maturation Index expresses the relative percent of parabasal*, intermediate, and superficial cells on a vaginal smear. The technologist counts 100 cells on a Papanicolaou smear, noting the number of individual cell types, then calculates the percent of each type. In short, she does a differential count of vaginal epithelial cells, in much the same way that she would count white blood cells.

As with white cells, shifts take place. The more estrogen, the more superficial cells. The less estrogen, the fewer superficial cells. Thus, a young woman at her estrogen peak before she ovulates will have about 80 percent superficial cells. But a postmenopausal patient with estrogen lack generally runs from 0 to 15 percent superficial cells. When a woman passes fifty, estrogen levels slowly fall, and the Maturation Index "shifts to the left," i.e., parabasal and intermediate cells predominate instead of superficial cells. The Figure gives you a rough idea of how the proportion of intermediate and superficial cells change in the aging woman.

*See Test Your Word Score, Page 175.



Figure—Relative percent of intermediate and superficial vaginal epithelial cells in women aged 30 to 60.

In the usual patient, 0.5 to 1.0 mg of daily diethylstilbestrol or 0.625 to 1.25 mg of daily premarin will result in a desired Maturation Index in three or four days. If the drug is discontinued, in about ten days the Index will drop to a 0 to 15 percent range of superficial cells. About two weeks after estrogens are stopped, postmenopausal symptoms may flare again. Patients whose ovaries are surgically removed may require a slightly higher dose of estrogen to maintain the percent of superficial cells in the 15 to 30 percent range than do women after a normal menopause.

Of course, nothing in medicine is without its problems. To get a good Maturation Index, you have to get a good smear. To do so, gently stroke with an applicator the upper third of the lateral vaginal wall. And as vaginal infections distort the differential, don't count on an accurate Maturation Index on a smear from a patient with trichomonal or monolial vaginitis. Finally, women who have been on digitalis preparations for more than two years often show a vaginal estrogen effect.[1]

But if you keep these matters in mind, the Maturation Index offers you an acceptable way to regulate estrogen doses. If you wish to read further about the effect of estrogen on the Maturation Index, I suggest these references.[2,3,4]

Richard L. Reece, M.D.
Minneapolis, Minnesota

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Roman Medicine

The most famous doctor in Rome was Galen. He was also the cockiest. He had all the answers, and went around looking for questions. Galen flatly stated that he cured everyone, though there were those who hinted he may have swept a few patients under the rug. Herbs were his favorite cure. He had an herb for every disease, and is even rumored to have fixed a broken leg by using an asparagus stalk as a splint. In a work called *De Simplicibus* he made everything sound simple, refusing even to admit that there was such a thing as a compound fracture.

He had some offbeat ideas about blood, which he thought so full of Natural Spirit, Vital Spirit, and Animal Spirit that there was no room for red and white corpuscles. Nevertheless, everyone took him as the final authority. If there was any question about a medical matter, people said with a shrug, "Ask Galen." Had he lived 1800 years later, he could have written a medical column and syndicated it in hundreds of newspapers.

Galen made a big point of numerology, emphasizing the importance of five senses, four elements, four humors, two sexes, one head, etc. Everyone agrees with him about the importance of two sexes and shudders at the thought of there being even one more or one fewer*

---

*Richard Armour: It All Started with Hippocrates, 1966.

A once-popular treatment for back pains was to have the seventh son of a seventh son stand or walk on the patient's back.





The pain of earache was allegedly relieved by holding a hot roasted onion to the ear.

For headache, a sovereign remedy was to wear a snakeskin round one's head.



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Contraindications: Edema; danger of cardiac decompensation; history or symptoms of peptic ulcer; renal, hepatic or cardiac damage; history of drug allergy, history of blood dyscrasia. The drug should not be given when the patient is senile or when other potent drugs are given concurrently. Large doses of the alka formulation are contraindicated in glaucoma.

Warning: If coumarin-type anticoagulants are given simultaneously, watch for excessive increase in prothrombin time. Instances of severe bleeding have occurred. Persistent or severe dyspepsia may indicate peptic ulcer; perform upper gastrointestinal x-ray diagnostic tests if drug is continued. Pyrazole compounds may potentiate the pharmacologic action of sulfonylurea, sulfonamide-type agents and insulin. Carefully observe patients receiving such therapy. Use with caution in the first trimester of pregnancy and in patients with thyroid disease.

Precautions: Before prescribing, carefully select patients, avoiding those responsive to routine measures as well as contraindicated patients. Obtain a detailed history and a complete physical and laboratory examination, including a blood count. Patients should not exceed recommended dosage, should be closely supervised and should be warned to discontinue the drug and report immediately if fever, sore throat, or mouth lesions (symptoms of blood dyscrasia); sudden weight gain (water retention), skin reactions; black or tarry stools or other evidence of intestinal hemorrhage occur. Make complete blood counts at weekly intervals during early therapy and at 2-week intervals thereafter. Discontinue the drug immediately and institute countermeasures if the white count changes significantly, granulocytes decrease, or immature forms appear. Use greater care in the elderly and in hypertensives.

Adverse Reactions: The more common are nausea and edema. Swelling of the ankles or face may minimized by withholding dietary salt, reduction in dosage or use of diuretics. In elderly patients and in those with hypertension the dru should be discontinued with the a pearance of edema. The drug has been associated with peptic ulcer and may reactivate a latent peptic ulcer. The patient should be instructed to take doses immediatel before or after meals or with milk minimize gastric upset. Drug rash occasionally occurs. If it does, promptly discontinue the drug. Agranulocytosis, exfoliative derm.

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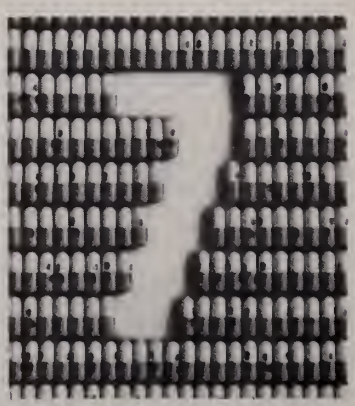
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Serious side effects can occur. Select patients carefully (particularly the elderly) and follow them closely in line with the drug's precautions, warnings and contraindications. Read the prescribing information. It's summarized below.

Stevens-Johnson syndrome, s syndrome (toxic necrotizing ermolysis), or a generalized gic reaction similar to serum ess may occur and require anent withdrawal of medica- Agranulocytosis can occur enly in spite of regular, repeated al white counts. Stomatitis rarely, salivary gland enlarge- may require cessation of treat- . Such patients should not ve subsequent courses of the . Vomiting, vertigo and languor occur. Leukemia and leukemoid ions have been reported. While efinitely attributable to the a causal relationship cannot be excluded. Thrombocytopenic purpura and aplastic anemia may occur. Confusional states, agitation, headache, blurred vision, optic neuritis and transient hearing loss have been reported, as have hyperglycemia, hepatitis, jaundice, hypersensitivity angiitis, pericarditis and several cases of anuria, glomerulonephritis and hematuria. With long-term use, reversible thyroid hyperplasia may occur infrequently. Moderate lowering of the red cell count due to hemodilution may occur.

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Before prescribing or administering, see Sandoz literature for full product information, including adverse reactions reported with phenothiazines. The following is a brief precautionary statement.

Contraindications: Severe central nervous system depression, comatose states from any cause, hypertensive or hypotensive heart disease of extreme degree.

Warnings: Administer cautiously to patients who have previously exhibited a hypersensitivity reaction (e.g., blood dyscrasias, jaundice) to phenothiazines. Phenothiazines are capable of potentiating central nervous system depressants (e.g., anesthetics, opiates, alcohol, etc.) as well as atropine and phosphorus insecticides. During pregnancy, administer only when necessary.

Precautions: There have been infrequent reports of leukopenia and/or agranulocytosis and convulsive seizures. In epileptic patients, anticonvulsant medication should also be maintained. Pigmentary retinopathy may be avoided by remaining within the recommended limits of dosage. Administer cautiously to patients participating in activities requiring complete mental alertness (e.g., driving). Orthostatic hypotension is more common in females than in males. Do not use epinephrine in treating drug-induced hypotension. Daily doses in excess of 300 mg. should be used only in severe neuropsychiatric conditions.

Adverse Reactions: *Central Nervous System*—Drowsiness, especially with large doses, early in treatment; infrequently, pseudoparkinsonism and other extrapyramidal symptoms; nocturnal confusion, hyperactivity, lethargy, psychotic reactions, restlessness, and headache. *Autonomic Nervous System*—Dryness of mouth, blurred vision; constipation, nausea, vomiting, diarrhea, nasal stuffiness, and pallor. *Endocrine System*—Galactorrhea, breast engorgement, amenorrhea, inhibition of ejaculation, and peripheral edema. *Skin*—Dermatitis and skin eruptions of the urticarial type, photosensitivity. *Cardiovascular System*—Changes in the terminal portion of the electrocardiogram have been observed in some patients receiving the phenothiazine tranquilizers, including Mellaril (thioridazine). While there is no evidence at present that these changes are in any way precursors of any significant disturbance of cardiac rhythm, several sudden and unexpected deaths apparently due to cardiac arrest have occurred in patients previously showing electrocardiographic changes. The use of periodic electrocardiograms has been proposed but would appear to be of questionable value as a predictive device. *Other*—A single case described as parotid swelling.

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Clinical Path Conference

Unexpected Postoperative Death

Case Report

THIS 67-YEAR-OLD WIDOW entered another hospital on December 9, 1968, with nausea, anorexia and back pain; she had been nauseated for six weeks and had forced herself to eat, but she had lost three pounds in that time span. An upper gastrointestinal series showed a fundal lesion of the stomach. On December 17 she was transferred to St. Barnabas Hospital to have this lesion removed.

Ten years before, she had been hospitalized for a bleeding peptic ulcer and treated conservatively. In October of 1966 she was treated for hypertension. In February of 1968, she again was admitted with a blood pressure of 210/135, cystitis, and recurrent urinary tract infection, all of which responded to drugs.

Physical examination revealed a pale, weak woman in no acute distress. Her blood pressure was 150/70 and her respirations 18 per minute. The abdomen was soft, flat and non-tender. Organs and masses were not palpated. There was no lymphadenopathy.

On December 18, 1968, a 4-cm. leiomyoma was removed from the posterior wall of the stomach near the esophago-gastric junction. The upper two thirds of the stomach was resected and a pyloroplasty performed. The patient did well during surgery.

On the first postoperative day, however, she developed fever, tachycardia, shallow breathing, and hypotension. The anesthesiologist started intermittent positive pressure breathing, using a Bennett respirator and mouthpiece. Two hours later, blood gas studies showed the following: pH 7.36, pCO_2 34, pO_2 46, O_2 saturation 78%. The following day slight abdominal distention and tenderness developed. Chest x-rays suggested some atelectasis at the right base and an inflammatory infiltrate in the left base with a small amount of pleural fluid. During the third postoperative day she improved. But then she again had respiratory difficulties. A tracheostomy was done. Respirations were assisted with the Bennett respirator, and the patient was restless and apprehensive. Generalized edema developed. On December 27 the abdomen was distended and tympanitic, and 300 cc of fecal-smelling drainage was removed from a nasogastric tube. A left upper quadrant peritoneal tap produced similar fluid. She expired a few hours after an emergency laparotomy.

Laboratory studies were as follows:

12/19	BUN 25, K 5.0, Na 142, Hgb 17, WBC 8,500
12/20	SGOT 30, Hgb 13.6, WBC 6,470
12/21	Two blood cultures—no growth
12/22	Na 128, K 4.0, Hgb 13.0, WBC 4,600
12/25	Na 140, K 3.0, Hgb 12.8, WBC 15,490
12/26	SSCG (Ca 7.3, P 3.9, glucose 215, BUN 31, cholesterol 80, T protein 4.0, albumin 1.2, bilirubin 0.9, alkaline phosphatase 55 mU/ml, LDH 250, SGOT 25)
12/27	Urine albumin 0.19 gm/24 hours, bilirubin 3.1, alkaline phosphatase 492 mU/ml., serum magnesium 3.9 mg%

Intravenous therapy included lactate ringers, 5% D/W, serum albumin and whole blood. Medications were cedilanid, valium, atarax, solucortef, tensilon, KCL and unipen. Postoperative urine outputs were good. Except for some atrial fibrillation on December 21, electrocardiogram findings showed nonspecific abnormalities.

Discussion

Dr. Harrison Farley:

This 67-year-old widow was hospitalized because of nausea, anorexia and back pain. She said she had lost three pounds, not a remarkable weight loss. Ten years before, she had had a bleeding ulcer which was treated conservatively and apparently cured.

As an x-ray on this admission showed a fundal lesion, I suppose we should see the film.

Dr. Frank Mork:

The abdominal x-ray discloses a well-circumscribed lesion of the gastric fundus that measures about 5 cm. Within this mass is a small ulcer crater. The lesion looks like an intramural tumor. Three types of such tumors exist. The most common is a leiomyoma; others are neurofibromas and lipomas.

Dr. Farley:

The lesion was a leiomyoma. To remove it, the surgeon resected the proximal two thirds of the stomach. I would be interested in knowing more about that procedure. Was the spleen removed?

Dr. Lyle Hay:

No. The esophagus was transected 2.5 cm above the esophago-gastric junction, and about 60% of the stomach was removed. The Hoffmeister technique was used to close the stomach to make the ends suitable for an anastomosis to the esophagus.

Dr. Farley:

The operation went well. After surgery the patient looked well in the recovery room. Trouble started the next day, and she died eight days later. On the first postoperative day she had respiratory difficulty, fever, a rapid pulse, and shallow breathing. To improve this situation required the use of an intermittent positive pressure breathing machine. On the second day after surgery her abdomen distended slightly and she experienced pain; but after gastric abdominal surgery it is usual to have tenderness and slight abdominal distention. However, Dr. Popowich is telling me that it "developed." I interpret that as something new and would be interested to know if the nasogastric tube was in place at this time?

Dr. John Popowich:

No, it was removed the day after surgery.

Dr. Farley:

I also note that chest x-rays showed atelectasis of the right base and infiltrate in the left base with small amounts of pleural fluid. At that time, she had a serum glutamic oxaloacetic transaminase of 30, a hemoglobin of 13.6, a white count of 6,470. I don't know if the white count drop was significant or not. Gram-negative bacteremia can produce a drop in the white count, and it declines further in another day or two. This was apparently considered; at least, blood cultures were done and showed no growth. Can we see the chest films?

Dr. Mork:

On December 19 there were linear bands of increased density at the right lung base which have the appearance of segmental atelectasis, and there was a little haziness of both costophrenic angles, particularly on the left. One would suspect a small amount of pleural fluid. On December 22 there were

increasing amounts of density at both costophrenic angles suggesting the further accumulation of pleural fluid.

Dr. Farley:

On the third postoperative day the patient improved, but suddenly she again deteriorated, and her respiratory troubles required a tracheostomy. At that time she was restless and apprehensive. This is a bad sign and suggests a pulmonary block in the trachea or a larger bronchus. Then she developed generalized edema. What this means, I don't know. It could be overloading with water, or it could be hypoproteinemia. After all, her albumin was 1.2. I also note that her urine albumin was 0.19 grams per 24 hours. Apparently she was not losing albumin through her kidneys. Could she have been extravasating albumin-rich fluid internally or losing it through her bowel? I don't know. At any rate, her abdomen became progressively distended, then tympanitic. Do the films of the abdomen show any free air?

Dr. Mork:

No.

Dr. Farley:

On the eighth postoperative day just before death, a nasogastric tube was inserted, and 300 cc of "fecal-smelling" fluid was removed. On the same day, a peritoneal tap was done, which produced the same fluid. So it seems clear that the patient had a communication between the intestinal lumen and the peritoneal cavity. The operation was probably done to repair this defect, but she died. Besides a breakdown of an anastomosis, what else could have happened to this woman? Why was she apprehensive? Could it have been due to low magnesium? Not likely, because one magnesium level was 3.9 mg %. Why did she suddenly stop breathing the day after surgery? I see she was given tensilon. If her breathing problem had been due to myasthenia gravis, she should have responded to that drug. Solucortef was also given, apparently with the thought that she might have adrenal apoplexy. Could I ask one other question, Doctor Popowich? Did she at any time after her surgery pass gas or stool? My children always ask me when I talk over the phone, "Why are you always asking about passing gas?" To the abdominal surgeon, it happens to be the most important thing in life.

Dr. Popowich:

Yes, she did pass liquid stool and flatus several days after surgery.

Dr. Farley:

In summary, we can say that a communication developed between the intestinal lumen and the peritoneal cavity. What caused it and where did it occur? Some event must have occurred to give dead intestine, a mesenteric thrombosis, for instance. In this case the mid-colic artery may have been injured. I would like to mention here something about the surgery itself. When the proximal end of the stomach is removed, the blood supply to the body of the stomach and the proximal end may be interfered with. If the left gastric artery is ligated and the epiploic artery is not carefully preserved, an ischemic bowel can result; hence the surgeon faces a dilemma, because in a gastrectomy for a benign lesion the complications may be worse than the lesion. Why did the anastomosis break down? Infection might be a reason. As in this patient, it would occur later in the course. Devascularization is a

good possibility. If it did not cause the breakdown, it may have contributed to the infection.

Finally, since this is a chronic passive congestion, I should mention another possible contributing factor. The patient did get intermittent positive pressure breathing through a mouthpiece. I don't know if that's endotracheal or the balloon. But if it were to be a mouthpiece alone, positive pressure in the remaining gastric pouch or stomach could have caused rupture through an already weakened anastomosis. A leak of an anastomotic line could have led to subsequent chest problems because of mediastinitis. Such an infection with an attendant chemical peritonitis could produce respiratory arrest and a respiratory or metabolic acidosis.

Dr. Farley's Diagnosis:

1. Leak of esophageal gastric anastomosis, possibly secondary to ischemia or infection.
2. Peritonitis.
3. Mediastinitis.

Discussion

Dr. Theodore Peterson:

On December 21 some atrial fibrillation was noted. Was the patient in heart failure? Did she gain weight from retained fluid?

Dr. Popowich:

On admission her weight was 130 pounds. Eleven days later she weighed 144 pounds.

Dr. Frank Johnson:

It is hard to attribute this patient's symptoms to a benign tumor. I was wondering if abdominal exploration indicated some other type of problem. Was there any laboratory evidence of injury to the pancreas?

Dr. Popowich:

During the operation the abdomen was explored and no evidence of pancreatitis existed. The operation went smoothly.

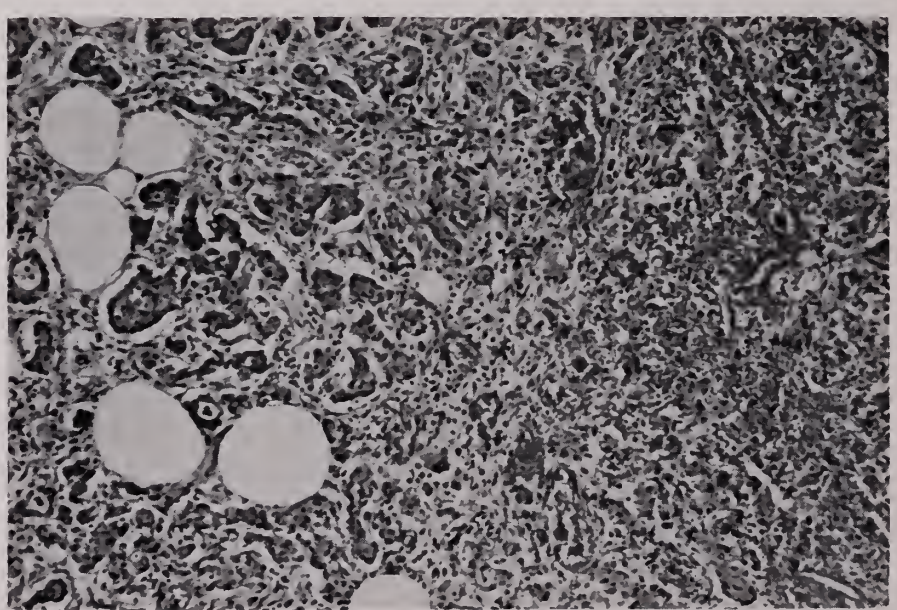


Fig. 1—High-power view of pancreas showing Isles of Langerhans on left and hemorrhage, necrosis, and inflammatory cells on right.

Dr. Jacob Strickler:

Did anybody do an amylase?

Dr. Popowich:

An amylase was not done.

Dr. Eugene Siruno:

I would like to point out that the albumin of this patient was 1.2. What could cause such a tremendous drop of albumin? That is a question the autopsy will have to answer.

Autopsy

Dr. Popowich:

Autopsy showed a stout elderly woman with a tracheostomy wound. In the right chest there were 700 cc of cloudy serous fluid; in the opposite chest, 400 cc of similar fluid. Both lungs showed gross emphysema, atelectasis and edema, with no evidence of bronchopneumonia or pneumonitis. There were no pulmonary thrombi in the large vessels. Cut sections of the lungs were not dramatic. The right diaphragm was elevated.

The abdominal cavity contained 600 cc of cloudy serosanguineous fluid. Generalized peritonitis was obvious. The pancreas showed diffuse edema, focal zones of hemorrhage, necrosis, and saponification of the surrounding fat (Figures 1 and 2). In other words, acute hemorrhagic necrotizing pancreatitis. The pyloroplasty site was intact. There was no leakage, and the suture line was good. In the area of the esophago-gastric anastomosis a small 5-mm defect was noted, although on close examination all sutures were intact.

Dr. Frank Johnson:

How did the defect come about, then?

Dr. Popowich:

At this point, perhaps I ought to call on Dr. Reece, who actually did the autopsy.

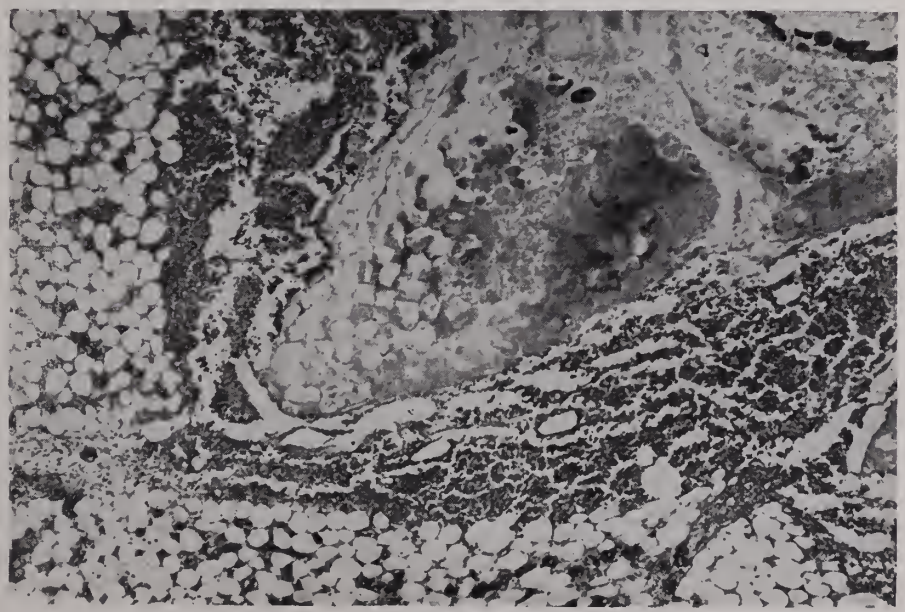


Fig. 2—Low-power view at edge of pancreas exhibiting saponified fat, dystrophic calcification, and inflammatory exudate.

Dr. Richard Reece:

As I understand it, a tube was inserted just before death. This went through the suture line. The anastomosis, weakened by infection and eaten away by pancreatic juice, just gave way. I think the defect is a late complication, not a contributing cause of death.

Dr. Popowich:

Here are some other microscopic sections. Here is a portion of liver. On the capsule of the liver is fibrinous exudate, which confirms the peritonitis. Next, sections show the thrombi in some of the small branches of the pulmonary artery. These thrombi are attached to the wall and are probably several days old (Figure 3). In addition to the thrombi are bone marrow emboli (Figure 3). These are secondary to the cardiac massage resuscitation and are a common finding after resuscitation with external cardiac massage. In about 30% of patients who die after massage, you will find marrow emboli in small pulmonary arteries, if you look thoroughly enough.[1]

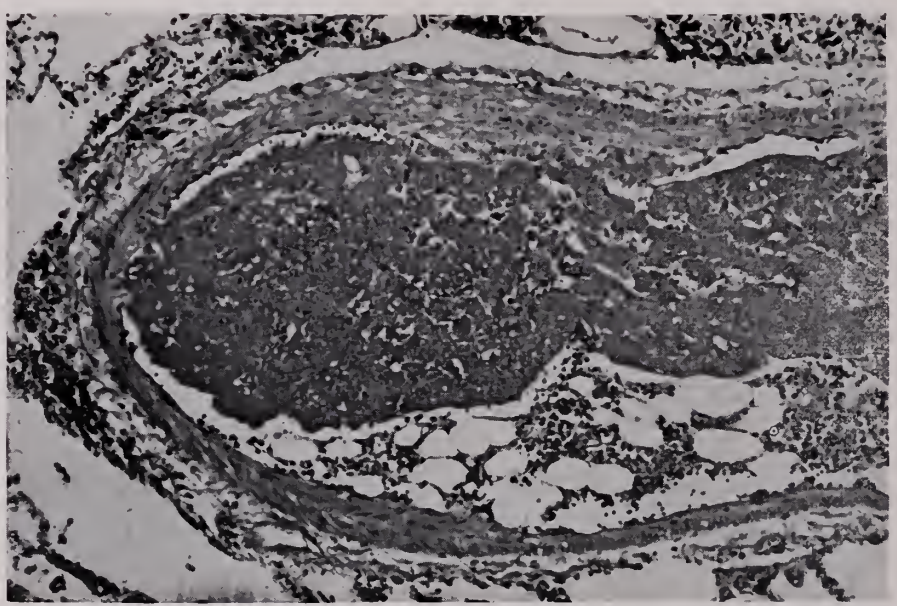


Fig. 3—Cross section of small pulmonary vessel showing adherent thrombus above and bone marrow embolus below.

Now a few comments on acute postoperative pancreatitis, which we feel this case represents. It is a rare occurrence, and the incidence in various series of pancreatitis is 3 to 23%. Causes of postoperative pancreatitis are mechanical injury, vascular injury, stagnation of duodenal contents, spasms of the musculature of pancreatic ducts. When it does occur, it commonly follows gallbladder or bileduct surgery, gastroduodenal surgery and splenectomy. Mayo Clinic investigators reported nine cases of fatal postoperative pancreatitis between 1940 and 1955.[2] One case followed gastric surgery, one followed pancreatic biopsy, and four were related to urologic procedures.

In summary, this patient had a partial gastric resection, stopped breathing the day after surgery, became diffusely edematous, then developed abdominal distention and died. Although at autopsy, necrotizing hemorrhagic pancreatitis with peritonitis was the principal finding, she did not have the typical clinical

picture of pancreatitis. One of the difficulties in diagnosing pancreatitis is that it may be relatively painless.[3] Besides, her respiratory emergency overshadowed and obscured her abdominal problems until near the end.

Given the benefit of hindsight, it is clear that the laboratory results offered clues as to the nature of her illness. What disease other than pancreatitis gives you a profound hypoalbuminemia and hypocalcemia? Also, she had an elevated lactic dehydrogenase, indicating tissue necrosis somewhere, and just before death, a sharply rising alkaline phosphatase. Both lactic dehydrogenase and alkaline phosphatase are known to rise in acute pancreatitis.

Autopsy Diagnoses

1. Acute necrotizing pancreatitis following gastric resection for benign leiomyoma of stomach.
2. Diffuse peritonitis.
3. Organizing thrombi in small pulmonary vessels.
4. Bone marrow emboli secondary to cardiac massage.
5. Hypoalbuminemia and hypocalcemia.
6. Small leak in gastric esophageal anastomosis.
7. Emphysema.

Richard L. Reece, M.D.
Minneapolis, Minnesota

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2. Ensrod, E. R.: Acute Postoperative Pancreatitis. Medical Times 94:755, 1966.
3. Dooner, H. P., and Aliaga, C.: Painless Acute Necrotic Pancreatitis. Arch Intern Med 116:828, 1965.

Changes in the Spectrum of Disease

Variations in the spectrum of disease which doctors are called upon to treat have always been a reality in medicine, although in the recent past, the changes in the patterns of illness have been far more rapid and extensive than anything ever seen before. Recently, a young graduate of our medical school left practice in a small Minnesota town to become part of a missionary medical group in a medically backward country in Southeast Asia. In leaving, he announced that he expected to see "more real pathology" in two weeks in Asia than he would see in his Minnesota practice in a year. From the balance of his remarks, it seemed evident that he was going off to find a "real medical practice," suggesting that practice as it now exists in Minnesota has so changed from the established pattern as to no longer be the genuine article. The changing pattern of illness from the dramatic epidemic scourges of yesteryear to the heavy predominance of the deterioration of age, malignancy, etc., has obviously affected medical practice, although not always necessarily in obvious ways.*

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*Magraw, Richard M., M.D.: Ferment in Medicine, 1966.

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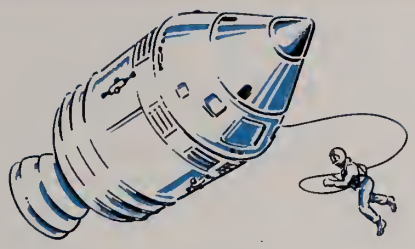
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(Continued to page 218)



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Advance

Antibiotic Sensitivity Patterns of Staphylococcus and Gram-Negative Bacteria

J. F. DEXTER, B.S.*
H. A. BATES, Ph.D.†
Minneapolis, Minnesota

MOST AUTHORITIES agree that coagulase positive *Staphylococcus* poses the most serious threat of bacterial disease in the hospital.[1,2] A second threat, growing in importance, is the enteric group of bacteria.[3] This group includes gram-negative, non-sporulating bacilli that live in the gastrointestinal tract of man or animals. Included are these species—*Salmonella, Shigella, Escherichia, Proteus,* and *Pseudomonas.*

From April 1967 to March 1968, *Escherichia, Proteus,* and *Pseudomonas* organisms comprised 35.7% of significant bacteria isolated at The Swedish Hospital, while coagulase positive *Staphylococcus* contributed only 17.8%. Because of the clinical importance of these four species of gram-negative bacteria, we studied: (1) how often they were isolated from clinical specimens, and (2) their sensitivity to various antibiotics.

Materials and Methods

Recording of Data

When our technologists received a specimen they recorded the name of the patient, medical record number, laboratory number, doctor's code number, source of specimen, type of microorganism(s) isolated, antibiogram(s), and other pertinent information on a printed form. This data was coded on an IBM punch card and tabulated at the Blue Cross computer center, St. Paul, Minnesota.

Antibiotic Sensitivity Tests

During the year of the study, our laboratory received 7,125 bacterial specimens and conducted antibiotic sensitivity tests on 3,387 bacteria isolated from these specimens. Routinely we used the disc diffusion method and carried it out with Baltimore Biological Laboratory, Inc., Baltimore, Maryland, (BBL), sensitivity agar and sensi-disc dispensers (R).

After inoculating the specimen onto suitable bacteriological media, the culture was incubated for 18 to 24 hours, aerobically or under 10% CO_2 at 37°C. The bacteria were inoculated into 1 ml of trypticase soy broth and incubated for one to two hours at 37°C. Next the culture was inoculated onto sensitivity agar.

The appropriate discs were dispensed onto the agar surface, and the plates incubated aerobically or under 10% CO_2 at 37°C. Results were read three to four hours later. The test was interpreted as follows: (1) sensitive to antibiotic—if zone of inhibition was present around disc; (2) resistant to antibiotic—if no inhibition zone was present around disc.

Routinely, by the disc method, *Staphylococcus* was tested against chloramphenicol (5 mcg), kanamycin (5 mcg), cephalothin (30 mcg), penicillin G (2 units), nafcillin (1 mcg), tetracycline (5 mcg), erythromycin (2 mcg), and lincomycin (2 mcg).

Gram-negative microorganisms were tested against chloramphenicol (5 mcg), colymycin (10 mcg), nitrofurantoin (100 mcg), sulfisoxazole (1.0 mg), kanamycin (5 mcg), cephalothin (30 mcg), naldixic acid (5 mcg), penicillin G (2 units), polycillin (10 mcg), polymyxin B (50 units), and tetracycline (5 mcg).

Disc method results were reported as either sensitive or resistant to the antiobiotic tested. In those cases where a more quantitative result was desired, a tube dilution test was done.[4] These results were reported as the minimum inhibitory concentration(s) (M.I.C.).

Specimens were obtained from hospitalized and outpatient clinical patients.

For results see Tables 1, 2 and 3.

Discussion and Conclusions

When this study started, the Hospital Drug and Chemotherapy Committee selected the antibiotics in the test batteries. In the case of

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TABLE 1

Antibiotic sensitivity of *Staphylococcus sp, E. coli, Proteus sp* and *Pseudomonas sp* isolated from various clinical specimens

	Staphylococcus sp[4]			E. coli[5]			Proteus sp[6]			Pseudomonas sp[7]		
Antibiotic tested	# organisms tested[1]	S[2]	R[3]	# organisms tested	S	R	# organisms tested	S	R	# organisms tested	S	R
Choramphenicol	592	575	17	757	727	40	294	277	17	143	18	125
Colymycin	22	8	14	767	735	32	294	32	262	144	127	17
Nitrofurantoin	22	4	18	765	750	15	294	278	16	144	20	124
Sulfisoxasole	21	2	19	767	33	734	294	16	278	144	26	118
Kanamycin	535	413	122	767	728	39	294	269	25	144	26	118
Cephalothin	598	593	5	767	742	25	294	270	24	143	18	125
Naldixic Acid	20	4	16	767	710	57	294	249	45	143	20	123
Penicillin G	600	418	182	764	26	741	294	98	196	144	12	132
Amphacillin	21	19	2	766	664	102	294	261	33	144	18	125
Nafcillin	580	553	27									
Polymyxin B	21	14	7	767	743	24	294	25	269	144	130	14
Tetracycline	597	472	125	767	639	128	294	25	269	144	22	122
Erythromycin	579	550	29									
Lincomycin	578	543	35									

1. Each organism was not tested against all antibiotics
2. Sensitive to antibiotic
3. Resistant to antibiotic
4. Isolated from 343 individual cases
5. Isolated from 563 individual cases
6. Isolated from 184 individual cases
7. Isolated from 90 individual cases

TABLE 2

Frequency of in-vitro antibiotic resistance* shown by Staphylococcus, *E. coli, Proteus sp*, and *Pseudomonas sp*

	Coagulase positive Staphylococcus†		E. coli‡		Proteus sp‡		Pseudomonas sp‡	
Resistant to:	# isolates	%	# isolates	%	# isolates	%	# isolates	%
No. antibiotics tested	313	52.2	1	.03	0	0	0	0
1 antibiotic	131	21.8	21	2.74	0	0	0	0
2 antibiotics	72	12.0	515	67.25	5	1.70	9	6.24
3 antibiotics	38	6.3	120	15.65	18	6.13	8	5.66
4 antibiotics	25	4.2	59	7.70	74	26.85	2	1.39
5 antibiotics	14	2.3	29	3.79	122	41.50	0	0
6 antibiotics	4	0.67	15	1.96	46	15.63	1	0.70
7 antibiotics	2	0.33	3	0.09	13	4.43	5	3.47
8 antibiotics	0	.00	3	0.09	9	3.06	17	11.80
9 antibiotics	1	0.07	1	0.03	2	0.68	102	70.80
10 antibiotics	0	.00	0	.00	0	.00	0	.00
11 antibiotics	0	.00	0	.00	0	.00	0	.00

*When tested by the described disc method

†Antibiotics tested—chloramphenicol, kanamycin, cephalothin, penicillin G, nafcillin, tetracycline, erythromycin, lincomycin

‡Antibiotics tested—chloramphenicol, nitrofurantoin, sulfisoxazole, kanamycin, cephalothin, naldixic acid, penicillin G, amphacillin, polymyxin B, tetracycline colymycin

Staphylococcus, these consisted mostly of older antibiotics, such as chloramphenicol, penicillin G, tetracycline and erythromycin. These had been used in The Swedish Hospital for years to treat *Staphylococcus* and other non-urinary tract infections and were effective against most organisms. Later, our studies disclosed that the newer antibiotics, kanamycin, cephalothin, nafcillin and lincomycin were also effective in vitro against most isolated *Staphylococci.* Our data further indicated that antibiograms of *Staphylococcus* isolated from hospitalized or outpatients' wounds or abcesses differed little.

Other bacteria studied also demonstrated interesting antibiotic patterns. For example, *E. coli* was resistant to sulfisoxazole. While in-vitro diffusion antibiotic sensitivity test results are often erratic with sulfas, the medium used in this study was considered by the manufacturer to produce reliable results. *E. coli* is most frequently isolated from urinary tract specimens. Over 90% of all the *E. coli* isolated from urine were resistant in vitro to sulfisoxazole. However, without post-treatment evaluation, what this laboratory finding means clinically remains in doubt. It was also found that 86% of *E. coli* isolated were sensitive to polycillin in vitro; whereas only 3% of such isolates were sensitive to penicillin G.

Only colymycin and polymyxin B were consistently effective in vitro against various *Pseudomonas* species. Of all those tested, 71% were resistant to nine of 11 antibiotics used. In those cases where the organism(s) was resistant to colymycin and/or polymyxin B, it was still sensitive to at least two of the other antibiotics used. In contrast, 42% of all the *Proteus* species isolated were resistant to five of 11 antibiotics tested, and 67% of *E. coli* were resistant to two of 11 antibiotics; whereas 52% of the *Staphylococcus* tested were sensitive to all antibiotics used. This data emphasizes the antibiotic resistance of enteric bacteria.

While excessive use of antibiotics is an important factor in the development of such resistance, a series of studies[5-7] have shown that, when different enteric bacteria inhabit the same environment, one species can transfer the antibiotic resistance factor (R) to another. In our study, specimens obtained from wounds or the lower respiratory tract frequently contained more than one kind of enteric bacteria. In a series of 714 such specimens, 19% contained significant numbers of other gram-

TABLE 3

Types of specimens from which *Staphylococcus sp, E. coli, Proteus sp* and *Pseudomonas sp* were isolated

Specimen source	Total # isolates	Staphylo-coccus	% of total isolates	E. coli	% of total isolates	Proteus sp	% of total isolates	Pseudo-monas sp	% of total isolates
Urine*	786	30	3.82	511	65.01	175	22.3	69	8.77
Wounds	658	321	48.65	189	28.70	93	14.12	55	8.36
Sputum	78	34	43.70	27	34.65	7	8.98	10	12.80
Blood	24	13	54.25	7	29.07	4	16.67	0	0
Various body fluids	30	13	43.40	14	46.70	2	6.67	1	3.33
Nose and or throat	156	144	92.30	12	7.70	0	0	0	0
Tissue†	6	2	33.30	4	66.67	0	0	0	0
Ear	18	9	50.00	1	5.56	0	0	8	44.44
Vaginal	12	2	16.68	1	8.35	7	58.35	2	16.68
Stool	33	27	81.75	3‡	9.10	3	9.10	0	0
Eye	9	8	89.0	0	0	1	10.10	0	0
Spinal fluid	1	0	0	1	100.00	0	0	0	0
TOTAL	1814	603	33.20	770	42.40	294	16.40	145	7.99

*Catheterized and non-catheterized specimens, cystoscopy

†Surgical specimens

‡Enteropathogenic *E. coli* isolated from children

negative bacteria. Many of these specimens came from patients with chronic infections. We did not attempt to detect the presence of R factor(s) though it may be important in antibiotic resistance.

Summary

Of 7,125 bacterial specimens received at The Swedish Hospital from April 1967 to March 1968, 3,387 were tested against antibiotic discs. Antibiotics most effective in vitro against *Staphylococcus* were cephalothin, chloramphenicol, nafcillin, erythromycin, and lincomycin. Though *E. coli* was sensitive to most antibiotics, it was extremely resistant to sulfisoxazole. Only colymycin and polymyxin B were consistently effective against *Pseudomonas*, while six antibiotics proved effective against *Proteus* species. Three enteric bacteria (*E. coli, Pseudomonas* and *Proteus*) were isolated twice as often as *Staphylococcus* species.

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2. "Infection Control in the Hospital." American Hospital Association. 840 North Shore Drive, Chicago, Ill. 60611.
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4. Bailey, R. W. and Scott, E. G.: "Diagnostic Microbiology." pp. 250-253. C. V. Mosby Company. St. Louis, Mo. 1962.
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Hypercalcemia-Hormonal Therapy Syndrome

Although hypercalcemia is most commonly associated with hyperparathyroidism, renal insufficiency, or prolonged or excessive intake of calcium salt and alkali, the hypercalcemic syndrome may also occur as a result of either androgenic or estrogenic therapy. The steroid hormones in particular exert a profound influence on calcium metabolism. Ergosterol, for example, is a recognized potent mobilizer of calcium. In observing the hypercalcemic effects of patients with metastatic osteolytic lesions who were treated with steroid hormones, Hermann and associates observed that a deleterious level of hypercalcemia also resulted from testosterone propionate and diethylstilbestrol. Similar observations were made by Gerbrandy and Hillendoarn in treating 45 patients with androgenic hormones.

The hypercalcemia is accompanied by characteristic symptoms of nausea, vomiting, dehydration, and toxemia. The outstanding pathologic feature consists of deposition of calcium in the renal tubules. The nephrocalcinosis leads to decreased function with retention of nitrogenous products.

Frequent tests for calciuria and serum calcium levels are essential in order to avoid acute spontaneous hypercalcemia.

Durham, Robert H.—Encyclopedia of Medical Syndromes
Hoeber Medical Division, Harper and Row, New York

A man who trims himself to suit everybody will soon whittle himself away.—Charles Schwab

---

Democracy is built by those who live to give and destroyed by those who live to get.—Swanson Newsette

Otolaryngology Clinics

The Emergency Treatment of Nosebleed*

A NOSEBLEED that does not stop spontaneously within a few minutes is an emergency. Prompt and effective treatment requires previous planning, organization, and certain essential equipment and supplies.

Equipment

Treatment of nosebleed is most convenient when the patient is seated in a chair, as the erect posture allows expectoration of blood with minimal delay. The patient's head should be supported by a headrest or by the physician's assistant. The patient with nosebleed is apprehensive, and without support it is difficult to avoid drawing away from a painful stimulus.

Adequate illumination is essential. Visualization of a deep, narrow recess such as the nose requires a system in which the light rays parallel the line of vision. This is provided by a concave head mirror or any one of several available head lamps. The concave mirror produces a beam that converges to a focal point and then diverges. Maximal illumination is achieved when the focal point is at the external nares (Figure 1).

*From the Journal of the Oklahoma State Medical Association, 62:135, April, 1969. By Permission.

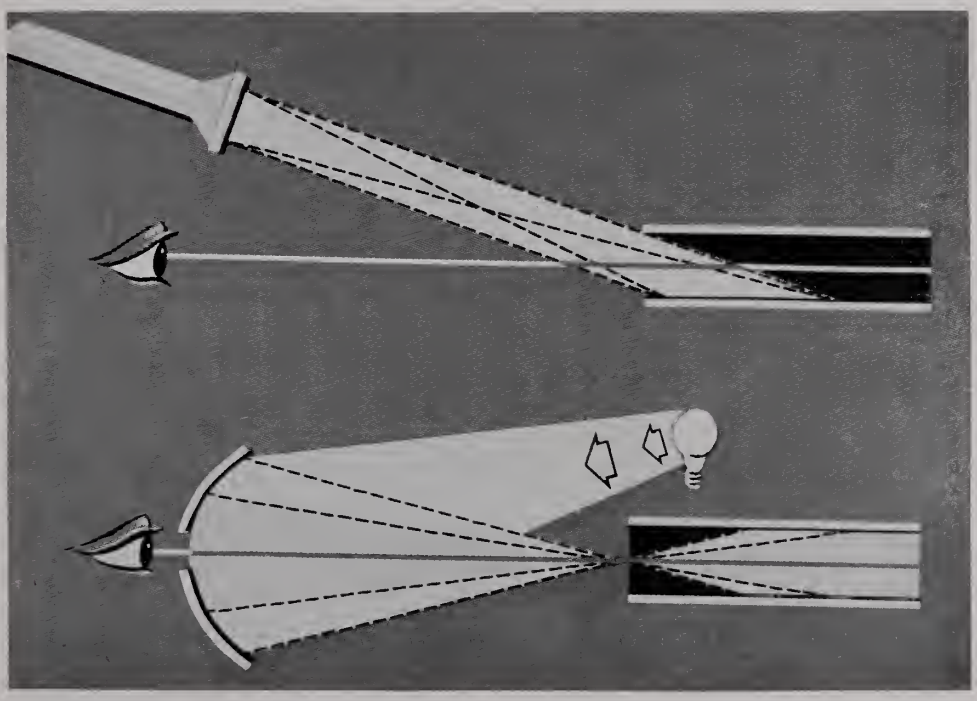


Fig. 1—Diagram showing visualization of deep cavity by reflected light. From Simonton, Kinsey M.: Diseases of the Eustachian Tube, Tympanic Membrane, and Middle Ear. In Maloney, W. H.: Otolaryngology. New York, Hoeber Medical Division, Harper & Row, Publishers, Inc. By permission of the publisher.

Adequate suction equipment is equally essential for examination of the bleeding nose. An electric-driven suction pump with a trap in the suction line to prevent blood from entering the pump is very satisfactory and is readily portable. Water-powered pumps permanently installed in the office provide adequate suction. The suction cannula should have an external diameter of approximately three mm and an internal diameter of two mm. This cannula will reach into most regions of the nose, and the lumen is adequate to pick up partially clotted blood. Smaller cannulae should be available for use in children or in narrow noses. Rubber catheters are not satisfactory, as they cannot be directed to a specific point within the nose. Two models of suitable cannulae are illustrated in Figure 2. The catheter illustrated is for placement of a postnasal pack. The dressing forceps illustrated is a six-inch bayonet type. The bayonet forceps is preferred, as it avoids blocking the vision with the fingers. Equipment and supplies are illustrated in Figure 3 and listed in Tables 1, 2, and 3.



Fig. 2—Equipment used in treatment of nosebleed.

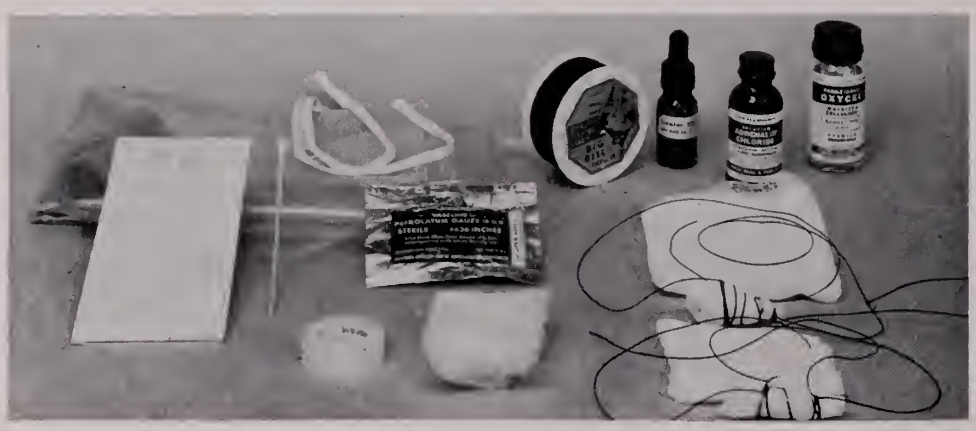


Fig. 3—Supplies used in treatment of nosebleed.

TABLE 1
Equipment Needed for Acute Nosebleed Program.

Chair with headrest	Nasal speculum (insulated)
Light	Nasal suction tips
Head mirror	Bayonet forceps
Suction	Cotton carrier (metal)
Cautery	Hemostat
Bib	Tongue blade
Basin	Catheter (No. 12 French)

TABLE 2
Materials Needed for Acute Nosebleed Program.

Absorbent cotton
"Vaseline" gauze (1 inch)
"Vaseline"
Oxycel
Gauze squares
Fishline
Adhesive tape

TABLE 3
Drugs and Other Aids Needed for Acute Nosebleed Program.

Morphine	Sedatives
Cocaine (10%, 9 ml) and	Blood
adrenaline (1/1,000, 1 ml)	Iron
Adrenaline (1/1,000)	Time
Silver nitrate	

Steps in Controlling Bleeding

The first step in controlling nosebleed is to minimize pain. Morphine given subcutaneously in adequate dosage is ideal. Topical anesthesia is achieved by use of cotton pledgets moistened in a solution of cocaine ten percent, nine parts, and 1/1,000 epinephrine, one part. These pledgets are placed in the nose during search for the bleeding area and serve to induce anesthesia, to shrink the mucosa, and to isolate the region of the nose under investigation.

The blood vessels of the nose traverse the submucosal tissues, forming dense plexuses of erectile tissue on the turbinates. The turbinates are rarely the site of bleeding. Rather, bleeding occurs from the anterior septum where the mucosa is dried excessively by respirated air, from the points of entry of major vessels, the anterior ethmoidal artery at the anterior part of the roof of the nose and the sphenopalatine artery at the posterosuperior region, and from a plexus of veins on the postero-inferior lateral wall under cover of the inferior turbinate, often referred to as Woodruff's plexus.

The second step in controlling nosebleed is to identify the site of the bleeding. When the patient is seated, blood in the nose tends to flow in a downward and backward course to the nasopharynx. The nose is approached at its antero-inferior quadrant where bleeding is almost always from the septum. During inspection, tampons eliminate flow from other regions of the nose. Suction is used to clear away excess blood and clots. After inspection of the antero-inferior region, the tampons, which are moistened in cocaine-adrenalin solution, are advanced to block flow from the posterior to the anterior part of the nose. Suction to clean the nose enables the anterosuperior quadrant

to be inspected for bleeding from the anterior ethmoid artery. If bleeding is not occurring from this artery, the tampons and suction are advanced to clear the posterosuperior region of the nose, and a search is made for a bleeding point from the sphenopalatine artery. Finally, the postero-inferior region is inspected (Figure 4).

With exception of the anterior septum, actual bleeding points are rarely seen. It is usually impossible to locate the source except during active bleeding. Extended search after bleeding has stopped is meddlesome.

The third step consists of controlling the bleeding point by use of cautery or packing. Topical anesthesia of adequate degree usually results from the cocaine-adrenalin pledget used during the inspection of the nose. Bleeding from small points on the anterior septum often stops with the application of these pledgets, but these points can be identified by a raised region on a superficial vessel. Bleeding is likely to recur if untreated. Cautery avoids the discomfort of packing the nose. Cautery with silver nitrate is inefficient for adults and its use is limited to children. Electrocoagulation by diathermy is preferred. Topical anesthesia is adequate for mucosal surfaces but should

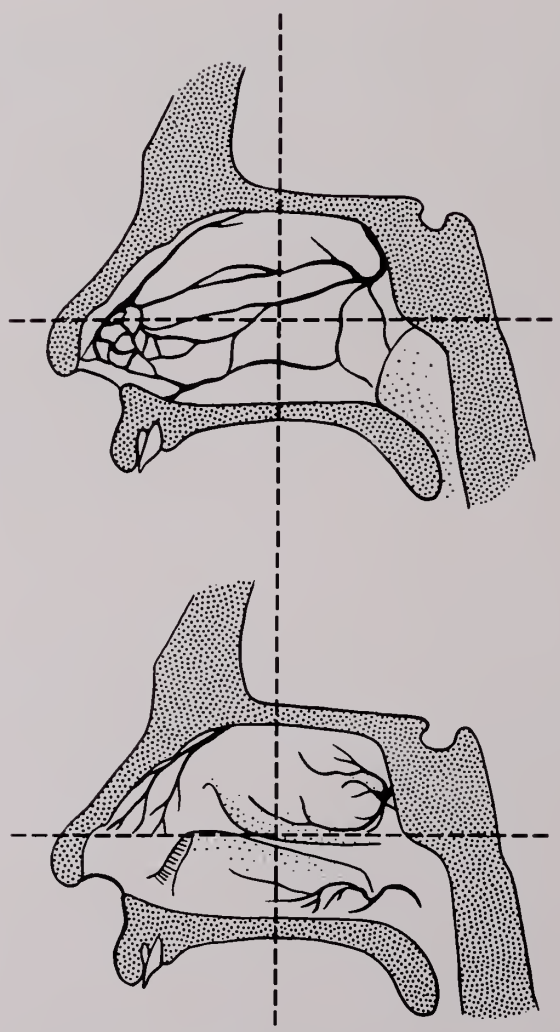


Fig. 4—Site of principal bleeding points in nose. Septum above, lateral wall below.

be supplemented by subcutaneous injection of an anesthetic agent when the bleeding point is near the skin-mucosal junction. The pointed cautery tip is held slightly away from the surface, and a spark gap is created. This technique avoids adhesion to the vessel and creation of bleeding as the tip is withdrawn. Adjacent vessels must be sealed before the actual bleeding point can be closed. A spark jumped to the bleeding point often restarts bleeding, making control much more difficult. Lubrication of Vaseline applied to the anterior nares twice daily helps avoid recurrence of anterior bleeding (Figure 5).

Packing

Packing may be used for anterior bleeding and is the method of choice for the other quadrants.

General rules for packing the nose are:

1. Apply an absorbable material (oxidized cellulose) to the bleeding region. This material remains when the pressure pack is removed.

2. Lubricate gauze-packs liberally with antibiotic ointment to minimize trauma to mucosa and to suppress bacterial growth.

3. Place the packing in layers to help maintain position and pressure. The pack should extend to the floor (or roof) of the nose in order to maintain pressure.

4. Leave pack in place five days. A pack once placed should remain until the vessel heals; five days is a safe interval.

5. Antibiotic coverage is desirable while the nose is packed.

The anterior ethmoidal artery is located in a narrow niche at the angle between the roof and anterior wall of the nose.

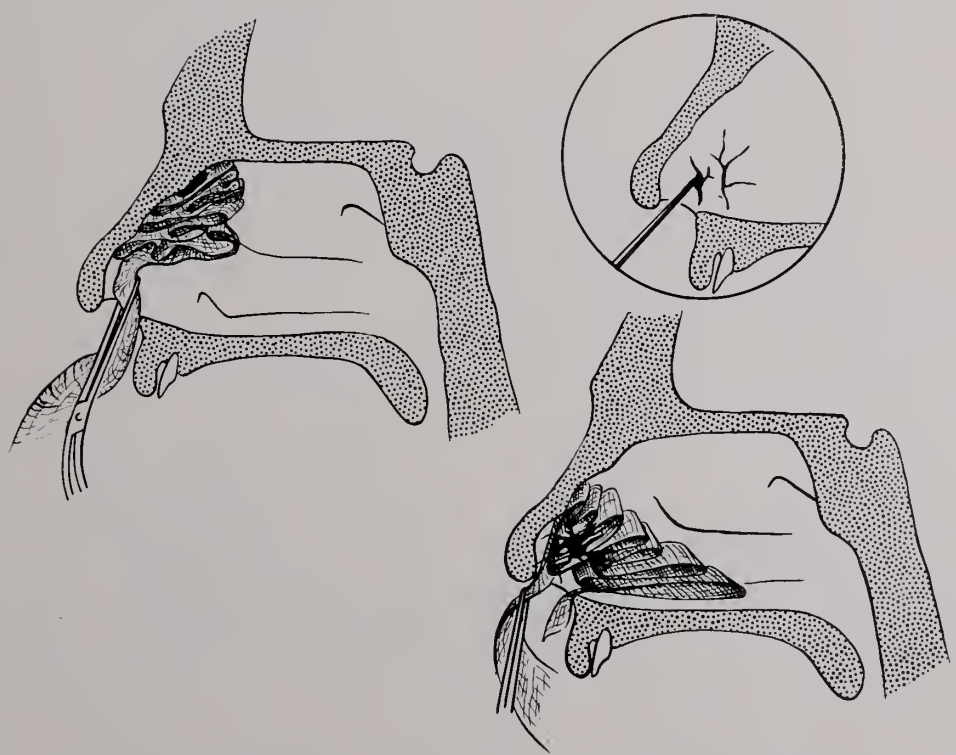


Fig. 5—Application of cautery and pack for bleeding from anterior region of nose.

Oxidized cellulose (Oxycel) is placed in the bleeding region and Vaseline gauze is forced against the Oxycel. When the pack reaches the level of the middle turbinate, a layering process is started. Each layer is pressed upward, while the pack is built down to the floor of the nose (Figure 5).

Packing for the posterior region of the nose is done from the floor up. A fold the full length of the floor of the nose is pressed to the floor. The second fold is two-thirds the length of the first, and the third fold is one-third the length of the first. The full-length fourth layer provides an anchor, and the process is repeated. This method builds the pack more rapidly at the back than at the front, maintaining working space at the anterior nares. When the pack reaches the level of the face of the sphenoid, gauze is forced against the face of the sphenoid between the pack and the roof of the nose until the nose is filled. This applies pressure to the sphenopalatine artery (Figure 6).

When the bleeding occurs under the cover of the inferior turbinate, the initial layers of this pack must be pressed laterally into the inferior meatus, in order to bring pressure on the bleeding area (Figure 7).

A pack that is properly constructed in layers and built up from the floor of the nose does not slide through the choana into the nasopharynx and provides an adequate base for applying pressure to bleeding points at the posterior region of the nose.

Severe irregularities of the nasal septum that prevent effective packing make submucous resection of the septum a part of hemorrhage control. Both nasal chambers must then be packed simultaneously to achieve pressure on the bleeding point (Figures 6 and 7).

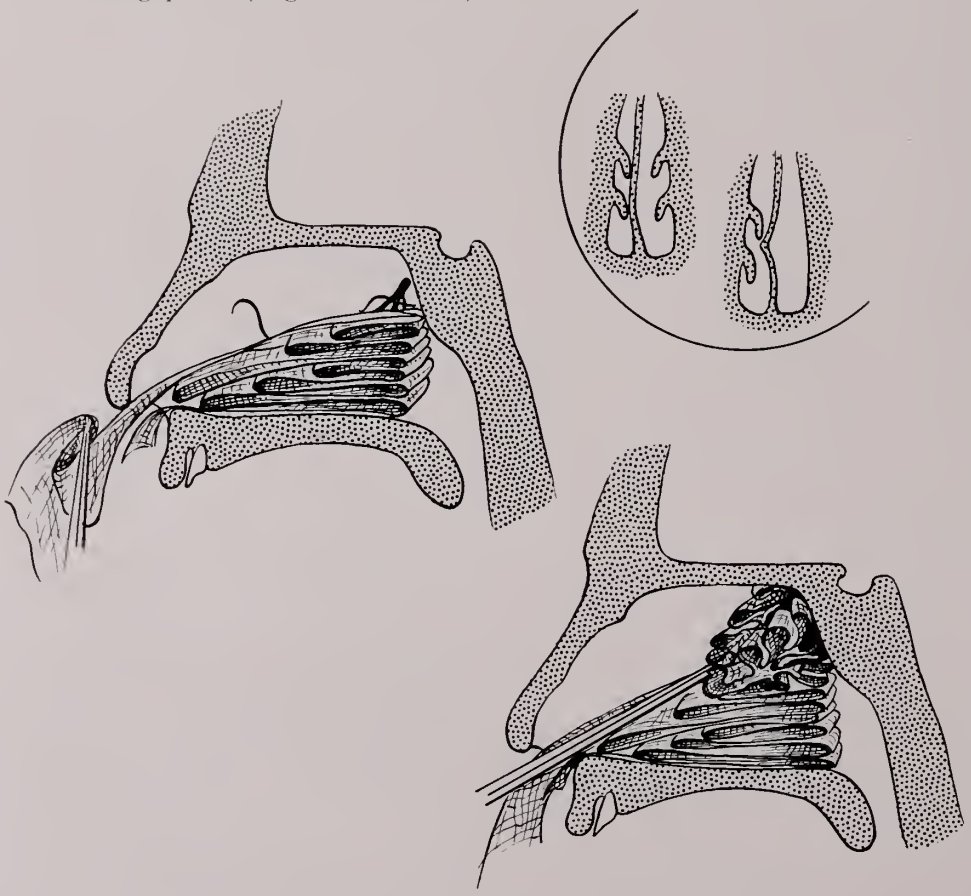


Fig. 6—Packing the sphenopalatine region. Effect of septal deviation.

In some patients, an overhang of the inferior turbinate prevents application of pressure to Woodruff's plexus. In these, it is necessary to fracture the inferior turbinate toward the septum and place the initial packing between the turbinate and the floor of the nose. The packing is then continued superior to the turbinate in order to apply adequate pressure. When the bleeding point in the inferior meatus is clearly seen, electrocoagulation may be used for its control (Figure 7).

A postnasal pack is seldom indicated in the treatment of nosebleed. As usually applied, this is a cylindric roll of gauze placed in the nasopharynx. The roll does not apply pressure to any bleeding point in the nose but is effective for control of bleeding from the nasopharynx.

A properly constructed postnasal pack is conical in shape, approximately one and one-half cm in diameter at its larger end. Three heavy strings are attached, two at the small end and one at the large end. A catheter passed through the nose and brought out the mouth is used to draw the double strings back through the nose. The third string comes out through the mouth and is taped to the cheek as an aid to removal of the pack. This pack presses against bleeders in the inferior meatus and can provide a base for packing the speno-ethmoid niche. The postnasal pack should be liberally impregnated with Vaseline before it is placed in order to reduce the possibility of restarting the bleeding when it is removed. Patients wearing postnasal packs should be watched for edema of the palate and for acute otitis media (Figure 8).

Hospital Care

Hospital care is desirable for the patient whose bleeding is not controlled

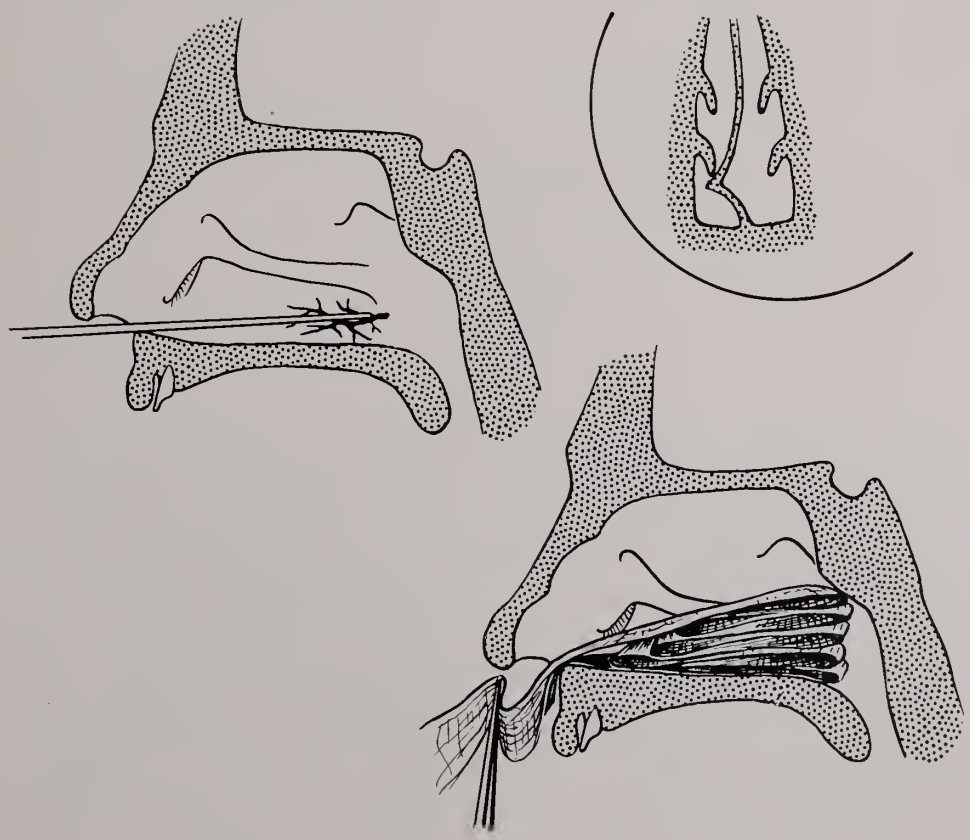


Fig. 7—Cautery and packing for postero-inferior quadrant of nose.

by the initial packing or for the patient whose blood is depleted by severe, intermittent bleeding. The patient should be put at complete bed rest for five days, with the head elevated, and given sedatives to allay apprehension and analgesics to relieve discomfort. Hematinic drugs are useful. Transfusion should be considered if hemoglobin values fall below 10 gm/100 ml blood.

When a patient presents a history of having bled through an existing pack, the pack should be removed and bed-rest instituted. Further investigation and packing are futile in the absence of active bleeding. In many instances no further bleeding occurs. Healing is encouraged by putting the nose at rest. A simple method is to reduce the air stream by a tape across the external nares.

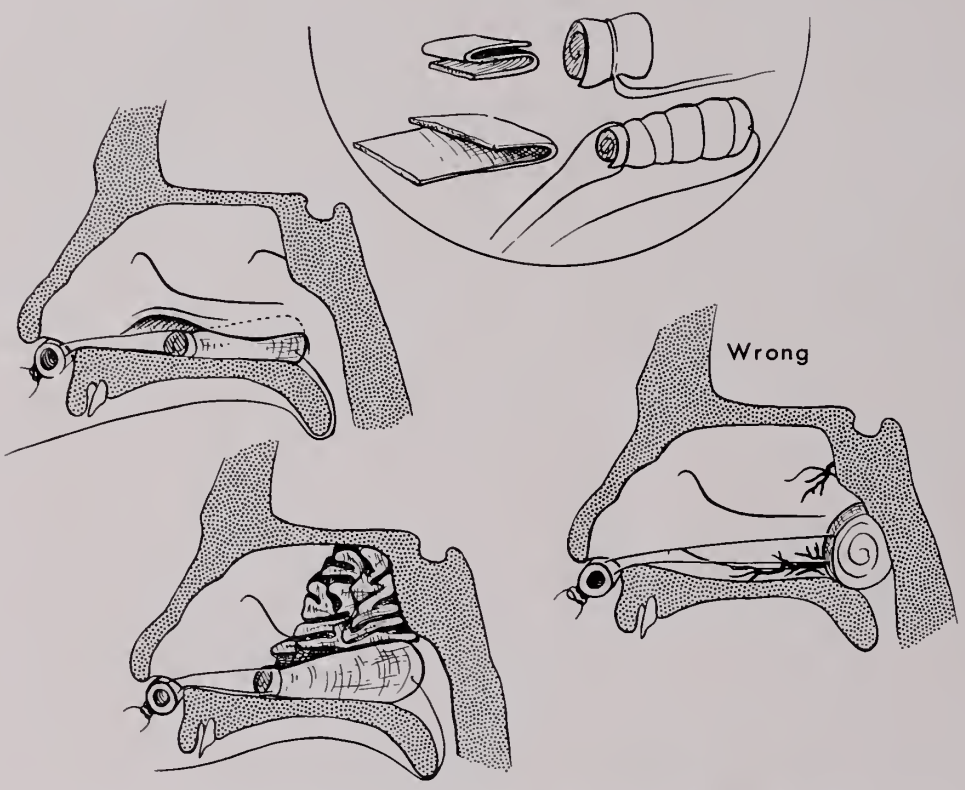


Fig. 8—Correct and incorrect methods of applying postnasal pack for treatment of nosebleed.

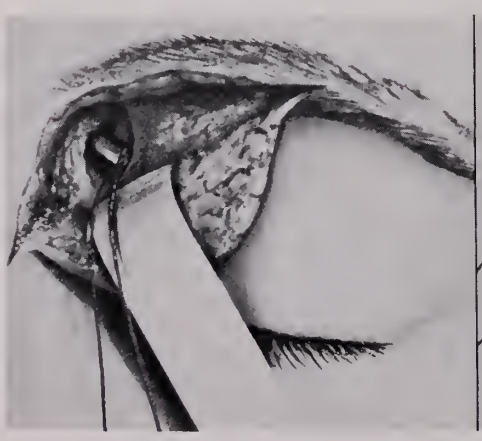


Fig. 9—Ligation of anterior ethmoidal artery.



Fig. 10—Ligation of external carotid artery.

Surgical Care

Ligation of vessels leading to the nose is required when bleeding is not controlled by packing. The anterior ethmoid artery is derived from the internal carotid artery and is readily approached in the orbit approximately two cm posterior to the inner canthus. The plane of dissection is between the periosteum and the bone at the roof and medial wall of the orbit (Figure 9). The arterial supply to the posterior region of the nose arises from the external carotid through the internal maxillary branch. The easiest access is through the neck where the external carotid may be ligated distal to its superior thyroid branch (Figure 10).

Drug Use

Many drugs have been used as aids in the treatment of nosebleed by improving the coagulation of blood. These usually give disappointing results, with the exception of vitamin K in patients who are receiving an anticoagulant and vitamin C in patients with deficiency of this vitamin.

Summary

A plan for treatment of acute nosebleed is presented. This plan includes a list of necessary equipment and supplies, the use of analgesia and topical anesthesia to make the patient comfortable, steps for examination of the bleeding nose, a method of packing the nose that allows application of pressure to the bleeding point, a brief discussion of hospital care, and the surgical approach for patients whose bleeding is not controlled by simpler methods.

Kinsey M. Simonton, M.D.*
Rochester, Minnesota

*Mayo Clinic and Mayo Foundation: Section of Otolaryngology and Rhinology.

Your Own Sphere of Influence

At a dinner for new faculty members at the university, I casually mentioned to the man in the next chair that "the facts had finally caught up with me," so that I quit smoking after getting up to over two packs a day and lost 75 pounds after achieving prodigious girth. The conversation moved promptly to other subjects, and I forgot all about it.

Nine months later, the same man walked into my office for a physical examination.

"Well, how do you like me?" he said. "Thirty pounds lighter, and no tobacco since September."

"Wonderful!" I said, trying to remember where I had seen him before.

"Don't you remember?" he went on. "That night at dinner—I figured that if you were convinced enough to *do* what you recommend, that was enough for me. And here I am!"*

*John E. Eichenlaub: The Minnesota Doctor's Home Treasury of Unusual Stress Easers, 1964.

Homeopathy

The vulgar quackeries drop off, atrophied, one after another. Homeopathy has long been encysted, and is carried on the body medical as quietly as an old wen.
—Oliver Wendell Holmes

Classified Advertisements

(Continued from page 200)

ST. PAUL—Spacious medical suite in new split-level building, part of a one block medical-dental complex adjacent to large shopping center. 1504 White Bear Avenue, 774-7144.

LARGE COMMUNITY HOSPITAL and medical center in the southwest needs a full time director of internal medicine service. Hospital has over 500 beds, internships and eight approved residency programs including internal medicine. Member of the Council of Teaching Hospitals of AAMC. Director of internal medicine is responsible for all activities related to internal medicine within the medical center. Annual compensation, $40,000. Write: MINNESOTA MEDICINE—444, 375 Jackson, St. Paul 55101.

EDUCATION PLUS: What midwestern high school of 170 boys currently has alumni at Harvard, Princeton, Swarthmore, M.I.T., McGill, London and Oxford (Rhodes Scholar), welcomes Americans, and produces great hockey teams? St. Johns-Ravenscourt School, Winnipeg 19, Manitoba. Headmaster: H. John P. Schaffter, M.A. (Cambridge), 204-453-3016.

WANTED: General practitioner to join two young general practitioners in well-established practice in suburban St. Paul. Excellent office space with lab, x-ray, and emergency room. Salary negotiable, with an association leading to early partnership opportunity. Write MINNESOTA MEDICINE 412, 375 Jackson St., St. Paul 55101.

GENERAL PRACTITIONER wanted to join well-established practitioner. New clinic building—90 miles east of St. Paul—city of 14,000. Early partnership with full hospital facilities. Ideal location. L. W. Picotte, M.D., Chippewa Falls, Wisconsin.

AVAILABLE: Well established General Practice for one or two physicians. Present physician is returning to graduate school. New, well equipped clinic located in a prosperous, progressive community of 1200, 28 miles from Downtown Minneapolis. Four hospitals in immediate vicinity. Any terms available. Contact R. E. Simms, Security State Bank of St. Michael, St. Michael, Minnesota. Telephone 612-673-2131.

DEPARTMENT CHIEF and General Practitioners for Medical-Surgical Department of 1900 bed JCAH approved Mental Hospital. Salary to $29,000 depending on training and experience. Excellent fringe benefits. College town. Summer-winter sports area. Near Interlachen National Music Camp. Small town peace and quiet—big city culture. Contact M. Duane Sommerness, M.D., Superintendent, Traverse City State Hospital, Traverse City, Michigan 49684. An equal opportunity employer.

WANTED: General Practitioner, Internist, Pediatrician, Orthopedic Surgeon for the Bemidji Clinic of Bemidji, Minnesota. Outdoor sports advantage second to none. The Bemidji Clinic now consists of four general practitioners, one internist, two general surgeons, one obstetrician, and one ophthalmologist. If interested contact Duane E. Carlson, Business Manager, Bemidji Clinic, Bemidji, Minnesota.

EXCEPTIONAL OPPORTUNITY (full time position) as Assistant Medical Director in Home Office of Northwestern National Life Insurance Co., Minneapolis, Minn. Preferably General Practitioner or Internist. Minimum experience required: 2 or 3 years' practice or residency. Five-day week with full fringe benefits including group life, hospitalization, major medical, disability income, non-contributory retirement plan and paid vacations. Salary open. Send curriculum vitae in first letter to Dr. John G. Walsh, Medical Director, NWNL, Box 20, Minneapolis Minn. 55440 or call 612-372-5446.

RECEPTIONIST, experienced, wants position in doctor's office. Can also do light lab and X-ray. Write: MINNESOTA MEDICINE—445, 375 Jackson St., St. Paul 55101.

A doctor examining an attractive new patient carefully, beamed, "Mrs. Atherton, I've got good news for you."

The patient said, "Pardon me, it's Miss Atherton."

"Oh," said the doctor. "Well, Miss Atherton, I've got bad news for you."

After his sixtieth year a man is more surprised to find himself right about something than he was at twenty to find he was wrong about something.—Strickland Gillilan

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Lots of folks wouldn't look as old as they do if they didn't act as young as they do.—Joe Digiovanni



Book Reviews

Those who don't read good books have no advantage over those who can't read them.—Family Circle

GREAT IDEAS IN THE HISTORY OF SURGERY—Leo M. Zimmerman and Ilza Veith. Dover Publications, Inc., New York. Price: $3.00; 587 pp. 2nd revised edition 1967.

The history of surgery is reviewed from Ancient Egypt (Papyrus Edwin Smith) to the school of Wangensteen by two well-known authorities. Excerpts from landmark papers and books are presented, discussed at length, and set in historical perspective. Thus all the great names in surgery pass in review and many lesser-known ones besides. Particular emphasis is placed on the interdependence of advances in surgery and in general medicine.

The value of the book is considerably enhanced by the numerous large illustrations from original sources. This is a handsome and readable book written for professionals, but with considerable appeal to the intelligent layman as well. Dover publications deserve high praise for making this classic available to a wide audience at an attractive price.

Martin J. Beckmann, M.D.
Providence, R. I.

CONFERENCE ON CELL CULTURES FOR VIRUS VACCINE PRODUCTION. National Institutes of Health, Monograph 29. Pages 595. Bethesda, Maryland, 1968. Chairman and Editor Dr. Donald J. Merchant.

This monograph is made up of papers presented before the Division of Biologics Standards, National Institutes of Health, December 6-8, 1967, at Bethesda, Maryland.

The conference was designed to provide information pertaining to cell culture as related to virus vaccines, made from primary cultures, diploid or finite cell lines, and continuous lines. Topics such as tumorigenicity of cells, presence of latent viruses or oncogenic agents as complicating factors, tissue culture vaccines developed from purified viruses, and certain nucleoprotein fractions were given consideration. Detection of latent, incomplete, associated and accessory viruses and other contaminants were discussed. Papers devoted to electron microscopy, immunofluorescence, specific immune serums, chemical and physical means of vaccine virus contaminants were given and commented upon in a constructive manner. Though the infective forms of cytomegalovirus, vaccina virus, and herpes virus have been demonstrated it was stressed that occult forms and other viruses incorporated in the genetic cell material may yet exist. Further, if human cells are used for vaccines, efforts should be made not only to detect noncytopathic viruses, virus-induced genetic changes or antigens, but also to develop techniques for disclosing background viruses in the vaccine itself.

The statement of Dr. George E. Foley (page 217) that "the precise nature of the biochemical defect(s) underlying neoplasia has not as yet been delineated," and the opinion expressed by Dr. S. Fedoroff as cited by Dr. Foley that "there are no in-vitro criteria which define tumorigenicity," show clearly that histopathologic criteria do not necessarily distinguish between non-ncoplastic and neoplastic cells.

The wide range of topics, the outstanding quality of papers and references should assure the monograph a prominent place on the desk of those active in the field of virology and immunoprophylaxis.

Emil Maro Schleicher, Ph.D.
Minneapolis, Minnesota

MORRIS FISHBEIN, M.D., AN AUTOBIOGRAPHY; Author: Morris Fishbein, M.D.; Publisher: Doubleday & Co., Inc., Garden City, New York; Price: $10.00; Pages: 505.

This is an excellent autobiography by an outstanding physician who has served his profession and his country well.

Morris Fishbein has contributed much to American medicine. Because of his sincerity and unquestionable integrity, coupled with honor and high ethics, the medical profession should be proud of and grateful for his noble service toward establishing an enviable image for all of us.

Except for being the Editor of the Journal of the American Medical Association, he has held no office in the Association; however, his favorable influence will no doubt be recorded in the history of American medicine.

The autobiography weaves no sequential, historical novel, but it makes for fascinating reading on almost every page. A few of the events of the author's life which might otherwise have remained a mystery are clarified in the perusal of this book.

A manifestation of one of his generous characteristics is evident in the index, wherein he has made reference to numerous friends and acquaintances to the exclusion of many other fascinating circumstances. A few additional references to some of his historical items, events and problems would have provided additional value to the spot-check reader.

Carl O. Rice, M.D.
Minneapolis, Minnesota

Meetings and Announcements

E. V. Allen Memorial Scholarships

Applications are now being accepted for the E. V. Allen Memorial Scholarships, open to junior and senior medical students attending medical schools in the United States or Canada. The scholarship provides three months of cardiovascular study at the Mayo Clinic, Rochester, as well as $1,000 award. Deadline for applications is April 1, 1970. Applicants will be notified by May 1, 1970. Brochures may be obtained by writing to Minnesota Heart Association, 4701 West 77th Street, Edina, Minnesota 55435.

Conference on Rural Health

23rd National Conference on Rural Health, April 9-10, 1970, Pfister Hotel and Tower, Milwaukee, Wisconsin. Contact: Council on Rural Health, American Medical Association, 535 North Dearborn Street, Chicago, Illinois 60610.

University of Wisconsin

The University of Wisconsin, Department of Postgraduate Medicine and Department of Pediatrics will sponsor a two and one-half day conference, March 12-14, 1970 on "Infectious Diseases."

For further information please write to Thomas C. Meyer, M.D., Chairman, Department of Postgraduate Medicine, 307 N. Charter, Madison, Wisconsin. 53706.

Nursing Course

The American Rehabilitation Foundation course *Nursing Care of the Long Term Patient* for R.N.'s will be offered March 2-18, April 6-22, June 15-July 1, September 14-30 and October 26-November 11.

Subject matter includes psycho-social aspects of nursing care, rehabilitation concepts, patient communications, nursing care plans, and preventive and maintenance nursing techniques.

Information about cost, living accommodations, and available stipends is available from: Ruth Stryker, R.N., M.A., American Rehabilitation Foundation, 1800 Chicago Avenue, Minneapolis, Minnesota 55404.

March Meetings

"Hibbing Clinical Seminars" Thursday, March 19, Hibbing General Hospital, Conference Room, Hibbing, Minnesota.

Diabetes Mellitus, Monday-Friday, March 23-27, "Diabetes Mellitus for Physicians", Diabetes Detection and Education Center, 915 East 15th Street, Minneapolis, Minnesota. Tuition: $100. AAGP Credit: 27 prescribed hours. Program Chairman: D. D. Etzwiler, M.D.

April Meetings

Spring Refresher, Wednesday-Thursday, April 1-2, Annual Meeting, Minnesota Academy of General Practice, Hotel Radisson, Minneapolis, Minnesota.

Head & Neck, Sunday-Tuesday, April 12-14, Society of Head and Neck Surgeons, Mayo Clinic, Rochester, Minnesota.

Occupational Medicine, Thursday, April 16, Minnesota Academy of Occupational Medicine and Surgery, Minneapolis Club, 729 Second Avenue South, Minneapolis, Minnesota. Program Chairman: Edwin G. Benjamin, M.D.

Continuation in Trauma, Friday, April 17, Nolte Center, University of Minnesota. Chairman: Dr. James House, "Trauma and Diseases of the Upper Extremities", Fee: $30.00. Limit: 80. AMA Credit: seven hours.

May Day Meeting, Saturday, April 18, "Infectious Diseases", Duluth Clinic, Ltd., Duluth, Minnesota. Location: London House, 2502 London Road, Duluth, Time: 10:00 a.m. to 5:00 p.m. Guest Speaker: Dr. Maxwell Finland, Minot, Professor of Medicine, emeritus, Harvard Medical School, Boston, Mass.



PHOTO BY VICTOR HAN





The concert was just underway,
When to the conductor's dismay
Cramps and diarrhea,
Did so quickly appear,
The maestro no longer could stay.

Because diarrhea with cramping, nausea, and painful straining can trike at the most inopportune time, it takes a comprehensive agent to treat the otal diarrheal syndrome and help get the patient back on the job. That's why o many physicians rely on Donnagel, especially during the fall and winter nonths when "flu" and viral gastroenteritis usually hit their peak.

Donnagel is much more than just a simple kaolin-pectin combination. t also contains the belladonna alkaloids to calm GI hypermotility and help elieve the distressing discomforts which so often accompany diarrhea. Certainly t's less expensive and more convenient than taking two medications. And the osage is lower too. Available in the handy 4-oz. plastic bottle at pharmacies verywhere on your prescription or recommendation.



or Diarrhea and its Discomforts

Donnagel®

ach fluid ounce contains: Kaolin, 6 Gm.; Pectin, 142.8 mg.; Hyoscyamine sulfate, .1037 mg.; Atropine sulfate, 0.0194 mg.; Hyoscine hydrobromide, 0.0065 mg.; odium benzoate (preservative), 60 mg.; Alcohol, 3.8%.

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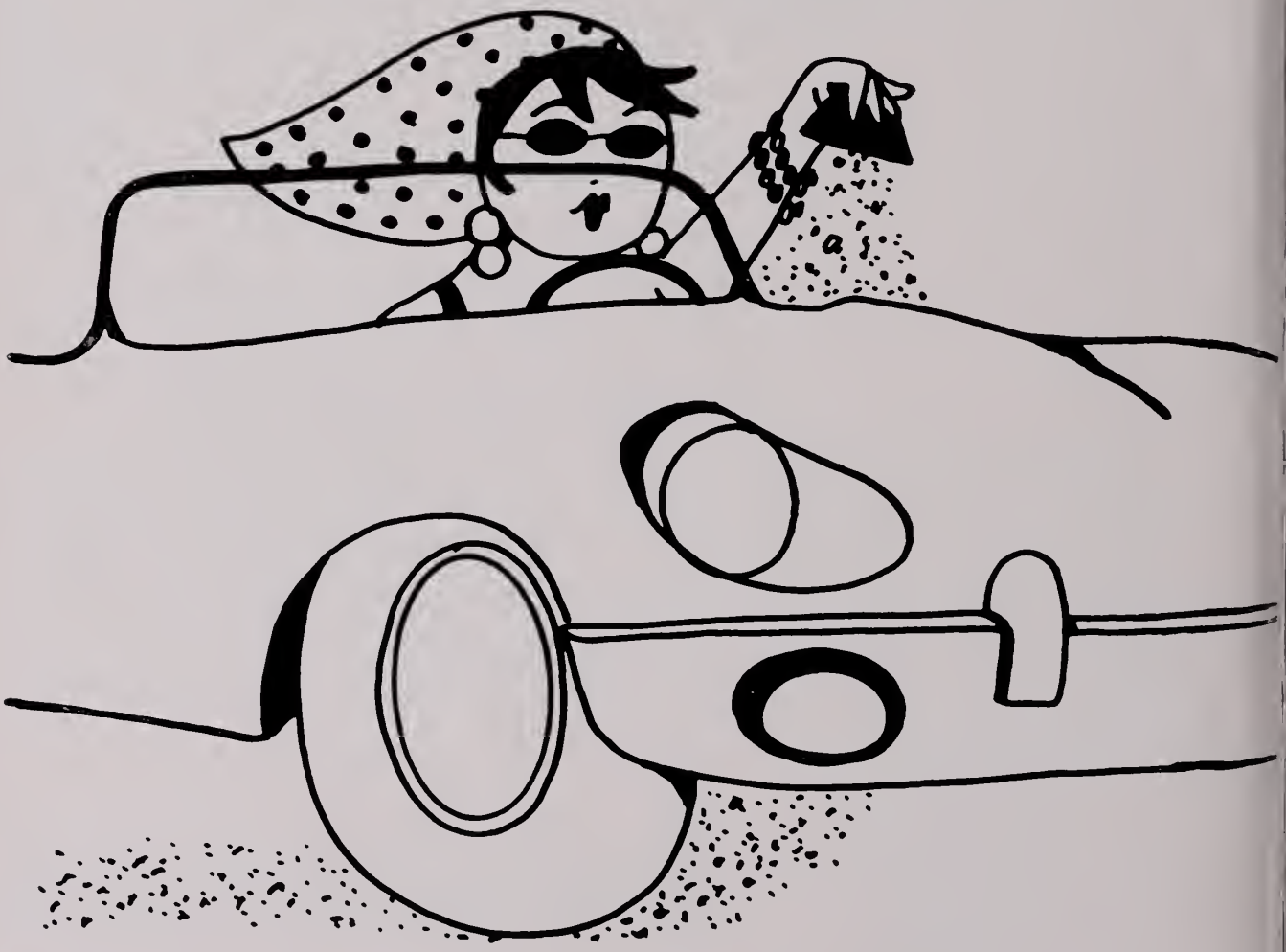
	Robitussin	Robitussin-DM	Robitussin A-C	Robitussin-PE	Cough Calmers
Expectorant	●	●	●	●	●
Demulcent	●	●	●	●	●
Cough Suppressant		●	●		●
Antihistamine			●		
Long-Acting (6-8 hours)		●			●
Nasal, Sinus Decongestant				●	
Non-narcotic	●	●		●	●

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MARY HAD AN ASHTRAY

by HENRY GIBSON

Mary had an ashtray
Full of ashes white as snow
And every time she drove her car
The tray would overflow.
She dumped it on the road one day
Which was against the rule.
The road is very ugly now
'Cause she was such a fool.



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Special Article

Hospital Costs and Hospital Charges

JOHN E. SMITH, M.D.*
Minneapolis, Minnesota

DOCTORS HAVE been the subject of satire since pictures were first drawn on cave walls. But the present wave of criticism started with the Medicare Act of 1965, blaming the physicians for the skyrocketing costs of the national health programs. Holding the line on fees would not decrease the criticism, for our fees make up less than 12% of the medicare dollar. Hospital costs make up the largest single item, accounting for about 60 percent of the Medicare total.

In the face of obscure claims about medical costs and irrational solutions for reducing them, some objective information appears essential.

Source of Materials

The figures in this paper were obtained from *Annual Guide Issue of Hospitals, Journal of the American Hospital Association,* published in August of each year. Table 1 comes from the 1969 issue which covers January through December 1968; Table 2 is derived from these same figures with 1967 figures added for comparison.

All hospitals in the five most populous Minnesota counties are listed in the first two tables. This study, however, will be concerned only with short-term hospitals in Hennepin and Anoka counties. Short-term means that over 50 percent of all patients admitted stay less than 30 days.

To obtain information on hospital charges (Table 5) I wrote to the staff presidents of each of the hospitals in the two counties. They calculated average charges for 25 consecutive, unselected cases from 1969 for each of the five illness categories. North Memorial was the only hospital which chose not to release the figures.

Method of Analysis for Tables 1 and 2

The cost/admission figures in Table 2 were calculated by dividing total hospital costs by the total number of admissions, not including newborns, as reported in Table 1.

The number of employee/patient figures in Table 2 were obtained by dividing the total number of employees (not including interns, residents, student nurses and other trainees) by the average patient census as reported in Table 1.

Preliminary Steps

I considered only Hennepin and Anoka county hospitals; I eliminated Kenny because it is long-term rehabilitation, Shriners because there was no data available, and the Naval Air Station Facility because its 12-bed size makes comparison invalid. Finally I ranked the remaining hospitals in order of increasing cost per admission, and patterns began to emerge (Table 3).

Cost Per Admission

Effect of Occupancy and Ancillary Service

All hospitals with a cost per admission of less than $500 are high census suburban hospitals with no intern or residency programs, but with active (and profitable) emergency rooms. A hospital census of over 80 percent means that for medicine and surgery there is usually a waiting list. From the standpoint of administrative efficiency, this is the ideal situation. Because of the waiting list, surgery tends to be elective in relatively healthy patients. Because of their short-term stay, a larger portion of their bill comes from charges for ancillary services, a high-profit item. Suburban dwellers are younger and therefore healthier; this also tends to shorten hospital stay.

Training Program

You have to get almost halfway through the ranking in Table 3 before coming to a hospital with a full intern, resident, and nurses' training program. The hospitals on the last half of the list tend to have complete training programs. Glenwood Hills is "out of place" because of its low census.

*President of the Medical Staff, St. Barnabas Hospital.

TABLE 1

Hospital	County	Beds	Admissions	Average Daily Census	% Occupancy	Expenses (Thousands)	Employees
	Olmsted						
Olmsted		70	2452	37	64	784	122
Rochester State		808	2052	616	76	3794	429
Methodist		573	19779	476	83	9692	1094
St. Marys		930	23340	716	77	11540	1367
	Ramsey						
Bethesda		298	9813	241	81	5157	611
Booth		11	350	4	36	93	30
Childrens		99	3815	70	70	2105	262
Gillette		136	945	88	57	2017	294
Midway		277	10880	251	90	5316	616
Miller		353	10790	292	82	4865	904
Mounds Park		136	3556	117	85	2467	247
Northern Pacific		138	2221	91	66	1323	203
Ramsey		585	10648	404	70	12084	1409
Riverview		75	3044	64	85	1591	188
St. Johns		321	12490	264	82	6292	687
St. Josephs		408	17024	308	75	7511	932
St. Lukes		360	8618	263	73	5929	?
	St. Louis						
USAF Dispensary		10	?	?	?	?	?
Miller		94	1358	63	67	1113	135
St. Lukes		395	12519	871	85	6522	871
St. Marys		344	13067	305	89	7138	912
	Anoka						
Mercy		151	7323	110	73	3351	307
Unity		139	7413	115	83	3486	358
	Hennepin						
Abbott		321	9736	215	69	5042	619
Deaconess		280	9375	229	82	5032	667
Eitel		129	4642	92	71	2334	302
Fairview Downtown		426	11136	339	80	6903	863
Fairview Southdale		227	12254	187	82	5255	647
Glenwood Hills		376	7528	255	68	5010	615
General		394	11903	331	84	9835	1031
Kenny		80	470	34	42	3375	292
Methodist		488	17506	371	76	8661	1013
Mt. Sinai		273	10762	224	82	6148	792
Naval Air Disp.		12	260	6	50	476	63
North Memorial		405	18271	314	86	8801	996
Northwestern		400	13082	349	87	7342	929
Shriners		60	279	46	76	?	80
St. Barnabas		310	11013	229	74	5800	771
St. Marys		505	17521	404	80	9393	1083
Swedish		429	13844	322	75	7737	927
University		816	15088	616	75	21087	2345
Veterans		981	11465	869	88	20509	1655

TABLE 2

Hospital	County	Average Cost per Admission (Hundreds of Dollars) (Year)	1967	1968	Employee per Patient Ratio (Year)	1967	1968
	Olmsted						
Olmsted			293	320		3.73	3.30
Rochester State			1875	1850		.78	.69
Methodist			429	490		2.51	2.29
St. Marys			418	495		1.88	1.90
	Ramsey						
Bethesda			405	526		2.72	2.53
Booth			234	266		5.4	7.5
Childrens			449	553		3.35	3.75
Gillette			1805	2130		2.87	3.34
Midway			453	489		2.26	2.45
Miller			636	727		2.92	3.10
Mounds Park			692	695		2.44	2.11
Northern Pacific			495	595		2.72	2.23
Ramsey			960	1160		3.32	3.49
Riverview			484	523		2.83	2.94
St. Johns			473	504		2.47	2.60
St. Josephs			472	442		2.56	3.02
St. Lukes			582	688		2.42	?
	St. Louis						
USAF Disp.			?	?		?	?
Miller			?	822		?	2.14
St. Lukes			470	520		2.77	2.59
St. Marys			476	546		3.18	2.99
	Anoka						
Mercy			?	457		?	2.79
Unity			?	470		?	3.11
	Hennepin						
Abbott			534	518		2.81	2.87
Deaconess			403	537		2.59	2.91
Eitel			483	504		2.95	3.28
Fairview Downtown			628	627		2.72	2.54
Fairview Southdale			393	433		2.69	3.46
Glenwood Hills			?	666		?	2.41
General			806	825		3.04	3.07
Kenny			656	718		7.80	8.59
Methodist			454	494		2.97	2.71
Mt. Sinai			468	571		3.27	3.54
Naval Air Station			?	1860		?	10.5
North Memorial			452	483		3.06	3.17
Northwestern			578	563		2.59	2.66
Shriners			?	?		?	?
St. Barnabas			457	526		3.04	3.37
St. Marys			455	535		2.93	2.68
Swedish			516	558		2.66	2.87
University			1093	1397		4.58	3.91
Veterans			3185	1790		5.15	1.90

Employee-Patient Ratio

Ranking the hospitals in order of increasing employee-to-patient ratio produces Table 4. Note that this table shows a completely different sequence from Table 3. Only two hospitals are even in the same half of the list in the two tables. Clearly, then, employee-to-patient ratio is not the main factor in producing a high or a low cost per admission. Apparently there is no pattern; so no conclusions, but some observations, are in order.

The Veterans Hospital

Cost Per Admission

At the Minneapolis Veterans Hospital, the employee/patient ratio is so low, and the cost/admission so high as to be almost unbelievable, especially when compared with the 1967 figures. That year they had 1,014 beds; 5,983 admissions; an average census of 328; a 32% occupancy; expenses of $19,037,000; and 1,693 employees. In 1968 they had 980 beds; 11,456 admissions; an average census of 869; and 89% occupancy; expenses of $20,509,000; and 1,655 employees.

Employees Per Patient

In 1967 the Veterans Hospital had 5.16 employees per patient, which easily made them the most densely staffed hospital in the two counties. But in 1968 they had only 1.90 employees per patient, making them the least densely staffed. In 1967 their cost per admission was $3,185, three times that of the University Hospital and seven times that of the average private hospital. In 1968 their cost was still the highest, but just slightly higher than the University and only three times that of the average private hospital.

If patients in the Veterans Hospital had been cared for in any community hospital, the government could have paid patients their regular salary while they were in the hospital and still have saved over $1,000 per admission. I can hear someone in Washington saying, "These figures are terrible, fix them up." And something was done, for the next year their admissions doubled while their employees decreased in number.

Rochester State Hospital

There is a group of hospitals whose admissions increased while their number of employees decreased: Olmsted County, Rochester State, Mounds Park, Downtown Fairview and Minneapolis Methodist. In 1967 Rochester State Hospital already had the lowest employee-to-patient ratio in the five counties studied: 0.78 employees per patient. By 1968, increasing admissions and a decreasing number of employees further lowered the ratio to 0.69 employees per patient. Doctors

TABLE 3

Hospital	Rank	% Occupancy	Cost/ Admission	Training Programs
Fairview SD	1	82	433	0 (None)
Mercy	2	73	457	0
Unity	3	83	470	0
North Memorial	4	86	483	0
Methodist	5	76	494	N (Nurses)
Eitel	6	71	504	0
Abbott	7	69	518	N
St. Barnabas	8	74	526	NIR (all) Nurses
St. Marys	9	80	535	NIR Interns
Deaconess	10	82	537	N Residents
Swedish	11	75	558	NIR
Northwestern	12	87	563	NIR (all)
Mt. Sinai	13	82	571	NIR
Fairview Downtown	14	80	627	NR (No Interns)
Glenwood Hills	15	68	666	0
General	16	84	825	NIR
University	17	75	1397	NIR
Veterans	18	88	1790	IR (No Nurses)

TABLE 4

Hospital	Employee/Patient Ratio	Rank
Veterans	1.90	1
Glenwood Hills	2.41	2
Fairview Downtown	2.54	3
Northwestern	2.66	4
St. Marys	2.68	5
Methodist	2.71	6
Mercy	2.79	7
Abbott	2.87	8
Swedish	2.87	9
Deaconess	2.91	10
General	3.07	11
Unity	3.11	12
North Memorial	3.17	13
Eitel	3.28	14
St. Barnabas	3.37	15
Fairview Southdale	3.46	16
Mt. Sinai	3.54	17
University	3.91	18

know that the highest employees-per-patient ratio does not always mean the most care per patient, but that ratio is less than the average hotel.

Training Programs and Outpatient Departments

Validity Affected by Variables

So far it would *appear* that employee-to-patient ratios are not related to the cost per admission. If the presence or absence of training programs is related, then hospitals thinking of entering the business of medical education should become aware of it. The relationship is there, but the validity is questionable. The cost per admission figure, based on total hospital expenses, is so gross as to be useless unless you are comparing hospitals with similar services, for it does not allow for length of stay, census, modern expensive equipment, depreciation, financial reserves, difficulty of cases handled and, most importantly, the outpatient departments.

Outpatient Service

The University, General, and Veterans Hospitals all have extensive outpatient departments, which markedly affects their cost per admission. If we were to use the same figures to arrive at a cost per outpatient visit, and similarly ignore the inpatient part of the costs, then the last three hospitals would be at the top of the list instead of at the bottom. Their outpatient department is the main difference. The 14.7 percent longer stay for teaching hospitals reported by PAS analysis also helps to explain why this kind of hospital has a higher cost/admission. No other valid conclusion can be drawn. Thus the apparent re'ationship between training programs and the cost per admission is meaningless because the many variables cannot be separated from the total hospital expenses.

Cost Accounting

These costs cannot be separated by means of the figures reported to the Journal of the American Hospital Association. More importantly, this cost separation is also not available to the governing boards of the hospitals. Cost accounting is not done in hospitals, though it has become routine and necessary in other businesses. Yet hospital governing boards must have this information if they are to intelligently decide whether to continue or start intern, resident, or nurses' training programs. They need it to decide whether to consolidate or expand or share services.

Charge Per Admission

I composed Table 5 with the hope that charge/admission figures would yield some information that was hidden in the cost/admission figures. The University, Veterans and General Hospitals are excluded because their services are different from private hospitals. (They are also excluded because they didn't answer my request for information.) Table 5

TABLE 5

Hospital	Appendectomy	T & A	Routine OB incl. nursery	Cholecystectomy	Myocardial infarction
Abbott	380	218	475	535	2142
Deaconess	471	205	492	715	1340
Eitel	565	251	431	1277	1838
Fairview Downtown	523	221	452	706	980
Fairview Southdale	441	233	448	916	2033
Glenwood Hills	644	240	377	1271	1136
Mercy	554	275	424	1097	1705
Methodist	370	216	373	774	1274
Mt. Sinai	354	218	504	907	1274
North Memorial	Refused Information				
Northwestern	554	184	436	840	1885
St. Barnabas	637	185	404	1062	1364
St. Marys	444	201	420	994	1736
Swedish	607	161	425	996	1016
Unity	544	255	492	688	1030

was a bit bulky, so the cost-of-illness figures for each hospital were added to get single, concise, workable units, which are arranged in ascending order in Table 6.

TABLE 6

Hospital	Total Charges	Rank	Training Programs
Glenwood Hills	2668	1	O
Fairview Downtown	2885	2	N R
Methodist	3008	3	N
Unity	3009	4	O
Swedish	3205	5	N R I
Deaconess	3223	6	N
Mt. Sinai	3257	7	N R I
St. Barnabas	3654	8	N R I
Abbott	3753	9	N
St. Marys	3797	10	N R I
Northwestern	3921	11	N R I
Mercy	4056	12	O
Fairview-Southdale	4070	13	O
Eitel	4364	14	O
North Memorial	Refused Information		

Key to column four:
nOne
*R*esident
*I*ntern
*N*urse

The rating obtained is a completely different one from that of the other two factors studied. The various training programs are again listed and, when ranked according to hospital charges, hospitals with training programs are scattered throughout the list. Now training programs obviously cost something. The Director of Medical Education at Mt. Sinai last year estimated the cost of his program at $750,000 per year. The estimate for the Metropolitan Medical Center Program for next year is $1,034,025. But this huge cost is not reflected in hospital charges to the patients unless hospitals without such programs are charging too much. Table 6 shows that hospitals with full training programs are scattered throughout and not in relation to the increasing charges.

What the Traffic Will Bear

The figures so far have been interesting but not helpful in answering the question: "Why do costs and charges vary so between hospitals with relatively similar services?" I have learned that hospital costs are not related to hospital charges and that neither are related to the number of employees, or to the presence or absence of training programs. In fact, hospital charges seem to be related only to what the traffic will bear. Suburban hospitals that should be able to operate at a lower cost have a bed rate within a dollar or two of the city hospitals which tend to have more complete services.

The Bed Costs

Actually the bed cost is a loss item at all hospitals and must be compensated for by "excess" profit from the ancillary services. This may account for the similarity of room rates. Actual charges for services, however, also vary throughout the county; and again without reason or pattern. The difference between average cholecystectomy charges (see Table 5) at the high and the low hospitals cannot be explained on the basis of a difference in medical practice between the two hospitals. The services at the two hospitals are relatively similar. Neither have training programs of any kind, their employee/patient ratios are within 0.17% of each other, and their cost/admission figures fall within $34.00 of each other; but their average charges for this procedure vary by 139%.

The Administrators and Cost Cutting

In searching about for the why of rising hospital costs, doctors tend to blame burgeoning administrative bureaucracy. This answer is simplistic and will not stand scrutiny outside of the staff room. Administrators don't deserve the blame, but it would be naive to expect them to work actively to decrease administrative costs. Parkinson's law and human nature both tend toward empire building. The function of administrators is to fashion a smoothly-running, expanding organization. This they do. Their main concern—their reason for being—is not to hold down costs. In fact, no one has this as his main concern.

Does Anyone Care About Costs?

Hospital costs interest trustees only from the standpoint of a balanced budget. They can continually solve their deficit problem by raising room rates. Doctors have a peripheral interest in hospital costs, but their main concern is, and should be, getting the patient well. Patients

don't care, for their insurance pays for it. The insurance companies don't care. They can simply raise the premiums. The people who buy the insurance don't care, for it is deducted, or the company pays half of it, or they really don't understand what they are paying for anyway.

The Feds are probably correct when they say that no one is directly concerned with holding down hospital costs. There is certainly little concern with the operating costs of the two Federal facilities in Hennepin County. But just because they don't keep down their own costs doesn't mean that they can't criticise costs of public and private hospitals. Until Medicare these hospitals were outside their jurisdiction; but now paying the piper entitles them to call the tune.

What Can Physicians Do?

Avoid Indiscriminate Rx

Physicians must become more concerned with hospital costs and charges. A simple way to begin would be to request copies of your patients' bills and study the charges. First, with patients' eyes to understand their complaints; then with an eye toward modifying your ordering practices. For example: ordering "Oxygen, if needed," costs the patient $3.00 per day for "Oxygen standby." Did you know that a room humidifier costs the patient $3.00 per day? Or that group therapy sessions on the psychiatry unit are as much as $15.00 per day over and above the $49.00 per-day cost of the room? Did you know that inhalation therapy costs up to $25.00 per day? If you order it, remember to discontinue the order as soon as the patient no longer needs it.

Physicians on Hospital Boards

Physicians should be active members of hospital boards and should be especially involved in preparing hospital budgets. They should work actively with other board members to develop meaningful accounting systems for hospitals.

Allow Flexibility of Routine Orders

Physicians should modify hospital rules to allow flexibility in routine admission and pre-surgical laboratory and x-ray studies. If the tests have been done that day in the doctor's office, they need not be repeated on admission to the hospital. This practice adds about twenty unnecessary dollars to the hospital bill. The Joint Commission usually gets the blame for this rule, but the Revised Standards for Hospital Accreditation (October 1969) p. 21 is clear on the subject.

Allow Out-of-Hospital Use of Facilities

"Medical care evaluation should include . . . the recognition of the medical practitioners' responsibility for the costs of health care. This review should cover . . . alternate use of out-of-hospital facilities and services. In addition, the services of out-of-hospital facilities for diagnosis and therapy should be reviewed." For once I am in complete agreement with the Joint Commission.

Educate Patients

Physicians should teach their patients that hospital medicine is expensive medicine. While it may be easier or more convenient to go to the hospital emergency room after they finish work, it doubles the cost. The use of partially trained hospital physicians, who often do not understand American English, also increases the cost and the need for protection. It is probably only a coincidence that these ancillary services are excellent generators of income.

Hospitals must not insist on laboratory and x-ray studies that are excessive by private practice standards, just to protect themselves. A proctoscopy done in the hospital is twice as expensive as one done in the office. Minor surgery is triple the cost in the hospital outpatient department. Certain laboratory tests are quadruple the cost in the hospital as when ordered through the office.

Hospital Pharmacy is Expensive

Drugs are more expensive when purchased through the hospital pharmacy. But, all too often, when these price differences are pointed out to patients they still want to go to the hospital. Out-of-pocket, immediate expense may even be less at the hospital, for there "My insurance will pay for it."

This use of hospital facilities "out of phase" in the chain of care has been fostered by in-

surance policies which cover only hospital services. Insurance companies thought this restrictive clause would save money, but it has had the opposite effect because patients would go to the hospital to receive this "benefit" when hospital treatment was not necessary.

A New Chain of Care?

We have to remind ourselves and train our patients to use the facility with the lowest possible cost. The chain should begin in the office; then home, nursing home, extended care, outpatient department, self-care, full-hospital care, and last special care. The patient should be able to move from level to level and back again as his needs dictate. Doctors in areas which do not have this full range of service should work actively to develop these facilities for all who need them.

A Medical Foundation

The Hennepin County Medical Society has been asked to sponsor a Medical Foundation. Similar plans have been operating in California for many years. The Foundation works with insurance companies to design acceptable policies, and provides the companies with a claims review. An acceptable policy would guarantee complete coverage for all necessary medical care wherever it is performed. This more realistic "chain of care" can mean a premium up to 14% lower than before. In California there is still enough of a surplus to pay the Foundation 4 percent of the premium as a service charge for claims review. The participating doctors agree to accept a relative value fee schedule as their maximum. This adequate and guaranteed fee is negotiated annually. The doctor's image becomes that of holding the line on costs, and he benefits from utilization and claims review done by his peers. Everyone benefits from the lower premiums with increased benefits. Insurance companies, patients, doctors, industries, labor; the Foundation's programs have something for everyone. This is the kind of activity which deserves our active support.

Thoughts While Shaving

Hospital services such as training programs, emergency rooms, and disaster drills are really community services. As such, all community members should support them through taxes rather than just those citizens who happen to be sick. Hospitals should consolidate some of these community services. Most hospitals should not have intern or resident training programs. Only a few should be required to maintain around the clock staffing of emergency rooms. Many nursing schools should be consolidated for class room teaching and dispersed for patient care.

Begin to think along these channels for your own hospital. Compare the figures. If your hospital charges more or can do it for less, find out why. Then spread the word so that our patients can also benefit.

Conclusions

1. Open staff community hospitals have assumed a role in teaching without materially affecting their charges. More information is needed in this area, for somebody is paying for the teaching. We must discover how much the various training programs add to the cost per patient day so that we can answer the question, "Is it worth it?"

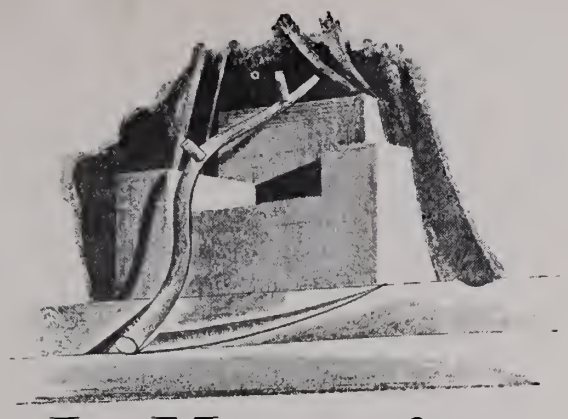
2. Hospitals should develop accounting procedures that would allow them to relate charges to costs. This would enable the governing boards to make intelligent long-range plans for the hospitals.

3. Physicians should increase their awareness of the cost part of their practice. They must, however, start now lest their attention be forcefully drawn to the subject by a Federal directive.

The body is but a pair of pincers set over a bellows and a stewpan and the whole fixed upon stilts.—Samuel Butler

---

Alcohol is something which very often puts the wreck in recreation.—The Johnson Way



In Memoriam

How beautiful is death, when earn'd by virtue!—Addison

JAMES L. BENEPE, M.D.

Dr. James L. Benepe, 67, St. Paul physician, died November 8, following a long illness. Born in St. Paul, Dr. Benepe lived most of his life in the city except for five years when he practiced medicine in Dent. He graduated from the University of Minnesota and Washington University School of Medicine and interned at the old Ancker Hospital.

He was a member of the American Academy of General Practice, the Ramsey County Medical Society, American Medical Association and the Minnesota State Medical Association.

Dr. Benepe is survived by his wife, two daughters, and three sons, one of whom is Dr. James L. Benepe, Jr. of Northampton, Massachusetts.

W. W. RIEKE, M.D.

Dr. Wellington W. Rieke, 63, Wayzata physician, died December 9. He had practiced medicine in Wayzata since 1933.

A graduate of the University of Minnesota Medical School, Dr. Rieke was a former chief of staff of the Abbott Hospital. He was a member of the Hennepin County Medical Society, the American Medical Association and the Minnesota State Medical Association. Dr. Rieke had also authored many papers on lake pollution and public health .

He is survived by his wife and two sons.

THOMAS J. KINSELLA. M.D.

Dr. Thomas Kinsella, 72, pioneer chest surgeon, died November 13. He was one of the leading authorities in the field of thoracic surgery for non-tubercular conditions of the chest and had written several works in connection with his specialty.

He was a past president of the Alumni Association Mayo Foundation, Hennepin County Medical Society, Minneapolis Surgical Society, Minnesota Trudeau Society, Minneapolis Academy of Medicine, Minnesota Academy of Medicine and the Minnesota Surgical Society. Dr. Kinsella also was a Fellow in the American College of Surgeons and a member of the American Thoracic Society, the American College of Chest Physicians, International College of Surgeons, Western Surgical Association, American Medical Association and the American Association for Thoracic Surgery. He was a Life Member and a 50 Club Member of the Minnesota State Medical Association.

In 1964, Dr. Kinsella was recipient of the St. Barnabas Bowl Award.

Dr. Kinsella is survived by his wife.

JAMES W. CRUMP, M.D.

Dr. James W. Crump, 83, St. Paul physician, was found dead in his office November 12. Born in Mississippi, he received his medical degree from the University of Iowa in 1914. He had practiced medicine in St. Paul since 1923.

Dr. Crump was a veteran member of the Board of the St. Paul Urban League and served as the League's president for several years. He was a member of the American Medical Association, the Ramsey County Medical Society, the American Academy of General Practice, and a 50 Club and Life Member of the Minnesota State Medical Association.

He is survived by his wife and a daughter.

CHARLES W. PARKER, M.D.

Dr. Charles Walter Parker, 57, Wadena radiologist, passed away November 6, following a long illness. Born in Olmsted Falls, Ohio. Dr. Parker attended the Universities of Michigan and Colorado.

He was a member of the Upper Mississippi Medical Society, the American Medical Association, the Minnesota State Medical Association and a Diplomate of the American Board of Radiology.

He is survived by his wife, two daughters and two sons.

WILLIAM L. PATTERSON, M.D.

Dr. William L. Patterson, 89, former superintendent of the Fergus Falls State Hospital, died December 13. A native of Nova Scotia and a graduate of Boston University, Dr. Patterson came to Fergus Falls in 1912.

He was a member of the Park Region Medical Society, the American Psychiatric Association, Minnesota Neurological and Psychiatric Society, the American Medical Association and a 50 Club and Life Member of the Minnesota State Medical Association.

EMERY C. BAYLEY, M.D.

Dr. Emery C. Bayley, 70, Lake City physician, died December 23. Born in Lake City, Dr. Bayley received his medical education at the University of Minnesota.

He was a former board member and treasurer of the Minnesota Medical Service, a former president of the Wabasha County Medical Society, a delegate to the Minnesota State Medical Association House of Delegates, a member of the American Medical Association, Academy of General Practice and served on the Board of Directors of the Lake City Hospital.

He is survived by his wife, one daughter, and three sons, one of whom is Dr. Bruce Bayley of Eau Claire, Wisconsin.

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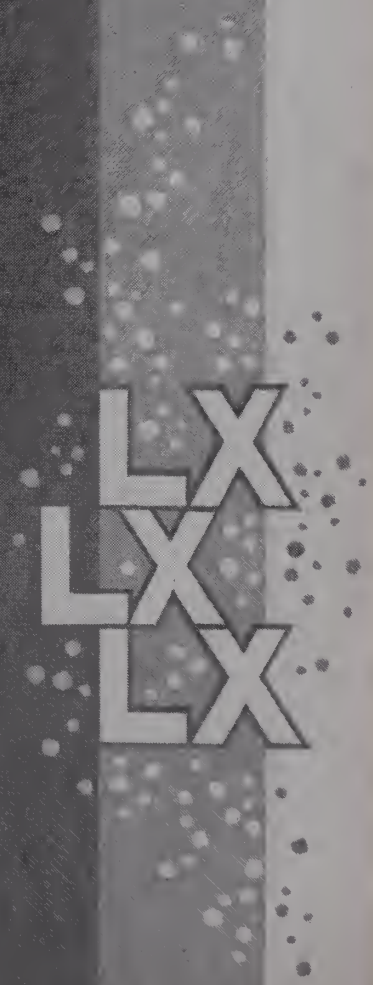
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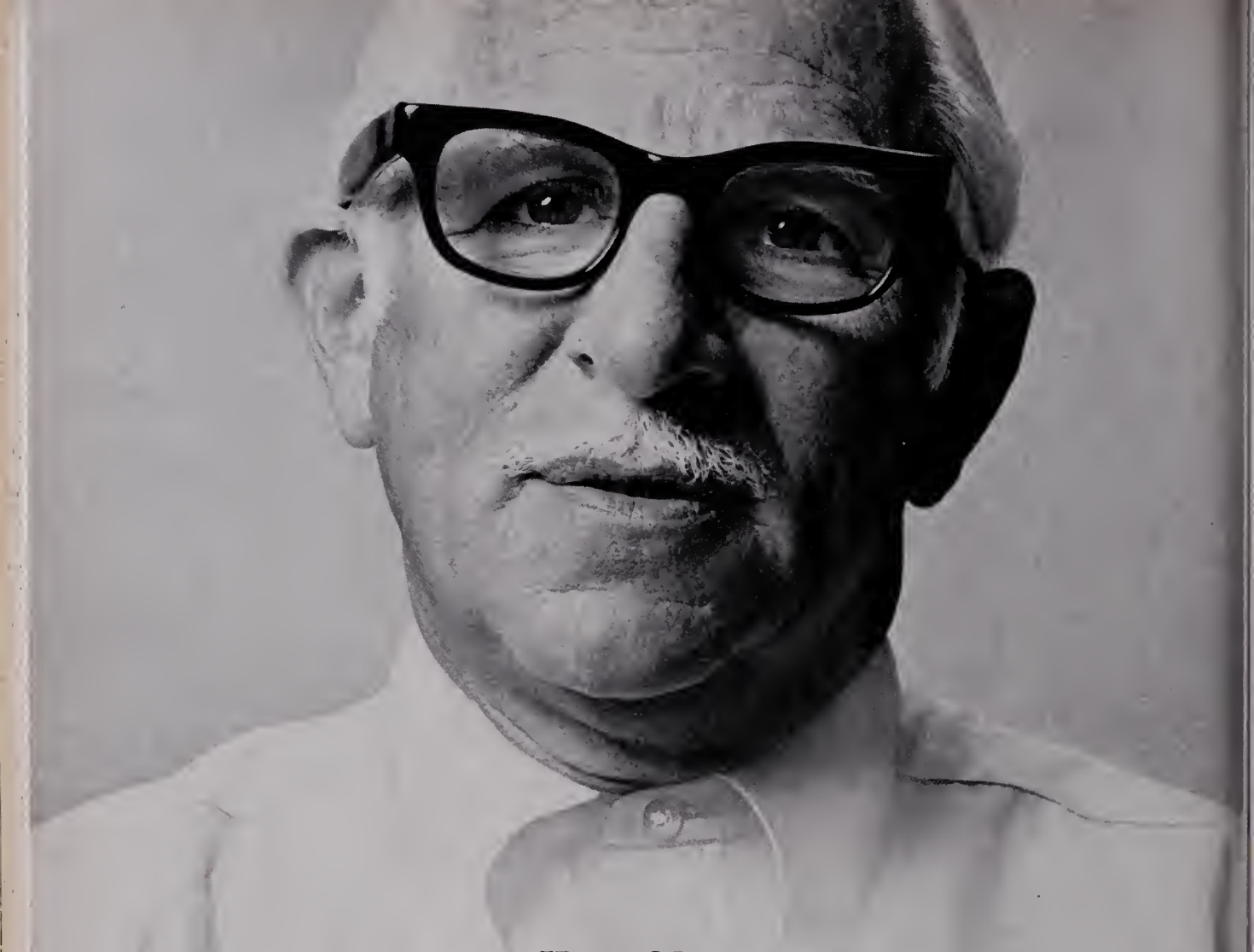
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Meet the President



Clyde E. Blackard, M.D.

President

Twin City Urological Society

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See the President's Letter, Page 241



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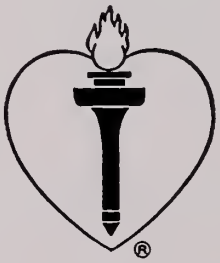
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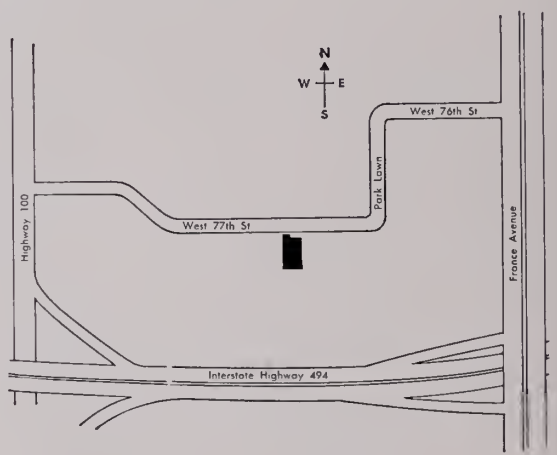
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President's Letter

TWIN CITY UROLOGISTS have made many important contributions to the specialty of Urology. Gilbert J. Thomas was not only the first Secretary of the American Board of Urology, but also the first President of the North Central Section of the American Urological Association in 1924. He was elected to the Presidency of the American Urological Association in 1937. Frederic E. B. Foley designed the first balloon-type retention catheter, reported an operative procedure for the correction of ureteropelvic strictures, and initiated a residency training program at the old Ancker Hospital in St. Paul. C. D. Creevy was Professor and Chairman of the Section of Urology at the University of Minnesota School of Medicine from 1934 to his retirement in December 1967. During these 33 years, he made many important contributions to the urological literature, but perhaps his greatest contribution was the introduction of a non-hemolytic irrigating solution for transurethral surgery. Theodore H. Sweetser, Sr., along with other surgeons in the Twin Cities, has done pioneering work in plastic reconstruction of extrophy of the bladder.

Urologists in the Minneapolis-St. Paul area are as highly trained and as competent as any group of urological surgeons in the United States. They are represented by the Twin City Urological Society which started as an informal gathering of six or seven local urologists in the early twenties. The Society has continued to grow, until today it is comprised of 44 Twin City members and 47 out-of-town urologists. The purpose of the Society, which holds monthly meetings throughout the Autumn, Winter and Spring, is to present both social and scientific programs. Representation with the County Medical Societies and other local groups is through specially appointed committees. The Twin City Society, by conducting scientific programs, attempts to improve urological care in the community.

What is the future for Urology in the Twin Cities? In June 1969, Edwin E. Fraley was appointed as Professor and Chairman of the Section of Urology at the University of Minnesota. In August 1969, the Urology Residency Training Programs at the Hennepin County General Hospital, the Veterans Administration Hospital and the University Hospitals were integrated. The St. Paul-Ramsey Hospital Urology Department remained independent but has nevertheless made important contributions to the weekly Combined Teaching Conferences.

A great deal of important basic and clinical research is being conducted by the Urology Sections at all of the teaching hospitals. For example, at the University of Minnesota Hospital, areas of basic investigation include viral oncology, tumor immunology and neurogenic vesical dysfunction, while at the Veterans Administration Hospital, the effects of diethylstilbestrol on the cardiovascular system of patients with prostatic carcinoma are being studied. Spheres of clinical research at these Hospitals include intrarenal obstructive uropathy, urinary incontinence, genitourinary cancer, the male transsexual and pediatric urological problems.

In addition to anticipating an exciting future in their specialty, Twin City urologists should be proud of their heritage and of the high standards of urological care in Minneapolis and St. Paul.

Clyde E. Blackard, M.D.
President
Twin City Urological Society

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Myelomeningocele

Current Concepts in the Treatment

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RECENT IMPROVEMENTS in treatment have made it possible to remove those afflicted with myelomeningocele from the back wards of custodial facilities to an independent life in open employment. However, the complexities of treatment may seem overwhelming to the parents, the patient and sometimes to the physician himself since the treatment program involves so many organ systems. Success depends on a combination of early neurosurgical treatment to prevent meningitis and hydrocephalus, continuing urological treatment to control incontinence and prevent hydronephrosis and renal death, and continuing orthopedic care to maintain straight backs and prevent crippling deformities especially of the hips and feet. This paper will survey some of the medical aspects as they are currently handled by the myelomeningocele clinic at Gillette State Hospital for crippled children.

Myelomeningocele is the most severe congenital anomaly consistent with life and, unfortunately, one of the most common. The reported incidence varies from two to four per 1,000 live births: a minimum of 120 affected babies born in Minnesota each year. Because of the high infant mortality of myelomeningocele only about 30 children with severe neurological damage would be expected to start school each year. In addition, another ten would have minimal neurological findings.

Myelomeningocele is the result of failure of fusion of the vertebral arches with dysplasia† of the spinal cord and its associated membranes with their subsequent herniation through this defect in the vertebral arch. The medullary plate, the nerve roots, and the dura are covered with only a thin layer of skin (Figure 1). In contrast, the meningocele has a normal cord and nerve root position with herniation of only the associated membrane (arachnoid and dura). Children with the latter defect are usually neurologically normal.

*Gillette State Hospital, St. Paul, Minnesota.
†See Test Your Word Score Page 277.

Disability Level

T12

Disability is related to the level of the neurological lesion. Approximately 5 percent of the patients will have the myelomeningocele above the level of T12. These patients have no motor power in the lower extremities, but the upper trunk and upper extremities are normal. Bowel and bladder function is impaired due to loss of innervation.

L1-L3

In approximately 10 percent of the patients, the lesion is in the L1-L3 level. These patients have some motor power present for hip flexion and hip adduction and, if the L3 nerve root is spared, some knee extension may also be present; again, there is bowel and bladder dysfunction.

L4-L5

If the intact level is below L4-L5, normal hip flexion and adduction and knee extension are present and there may be some dorsiflexion of the ankle. Approximately 50 percent of the cases fall into this group; bowel and bladder are also affected at this level.

S1-S2

In 20 percent the lesion is at the S1-S2 region; the hip now has weak abduction but usually no extension; knee flexion and extension are good and there is dorsiflexion of the ankle with weak plantar flexion and some toe movement.

Lower Sacrum

The remaining 15 percent of the cases have the lesion in the lower sacral region. Motor power is normal or nearly normal in the lower extremities; however, there is perianal hypesthesia. Bowel and bladder dysfunction persists in nearly all myelomeningocele patients.

Neurosurgical Problems

The increase in life span and the probability of a useful existence are the direct result of the success of modern neurosurgical techniques. The two problems, the herniated sac and impending hydrocephalus, are interdependent and usually ventriculo-atrial shunting is required soon after closure of the sac. The advent of shunts such as the Holter or Pudenz valve type has profoundly changed the natural history of inevitable hydrocephalus. Following shunting, close follow-up is needed, as the atrial limb of the shunt will pull out of the heart as the child grows. Thus, several procedures may be needed to maintain the effectiveness of the shunt.

Proper judgment in the management of the myelomeningocele child is paramount, especially during the first few months of life. Some centers make a strong case for immediate closure of the sac, while others wait many months to determine which children will survive. Some neurosurgeons perform the shunting first, with closure of the sac to follow. In Minnesota, an intermediate approach is ad-

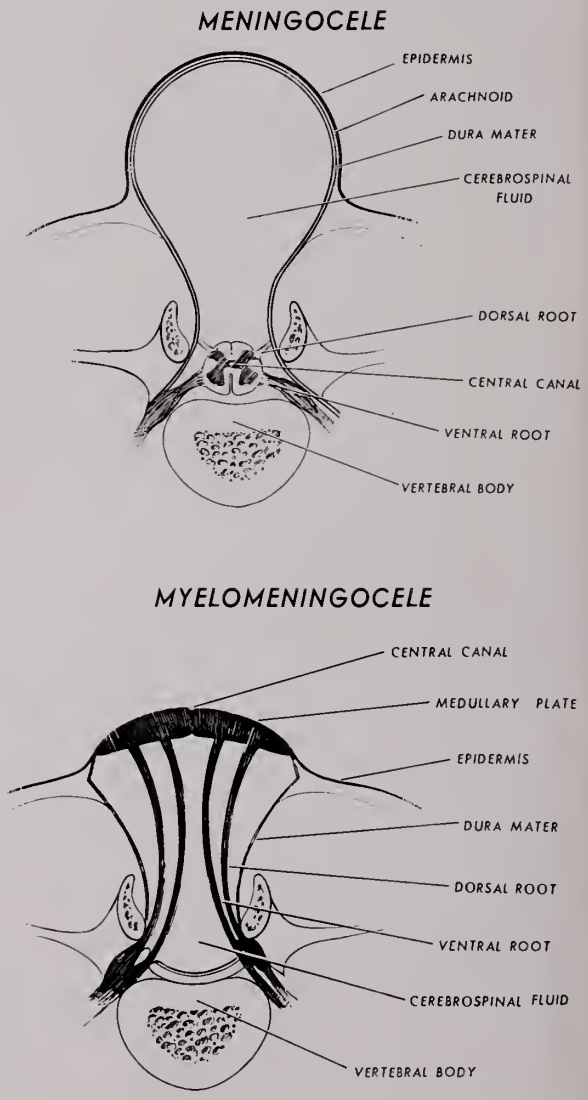


Fig. 1—These drawings illustrate the differences between a meningocele and myelomeningocele. In the latter, the cord, in addition to its coverings, has herinated through the posterior bony defect.

vocated; usually, the sac is closed soon after birth and shunting is delayed until signs of hydrocephalus begin to develop. Individualization is extremely critical in all of the decisions.

At the time of the sac closure a careful search must be made for a projecting spike of bone or cartilage (diastematomyelia) anchoring the cord. This is reported as a very rare condition but it is quite frequently associated with myelomeningocele.

Urologic Problems

A neurogenic bladder was present in 74 of 75 children seen with myelomeningocele at Gillette State Hospital. The hazards of untreated neurogenic vesical dysfunction are progressive hydronephrosis and pyelonephritis (Figure 2). In addition, urinary incontinence occurs and is unacceptable to parents, patients, and teachers alike. Unlike the orthopedic problems, neurogenic bladder disability does not depend on the level of the spinal cord dysplasia.

Hydronephrosis

Only 13 percent of the preschool children had hydronephrosis when first seen; but after age six it was four times as common (Figure 3A). Since the rate of hydronephrosis in-

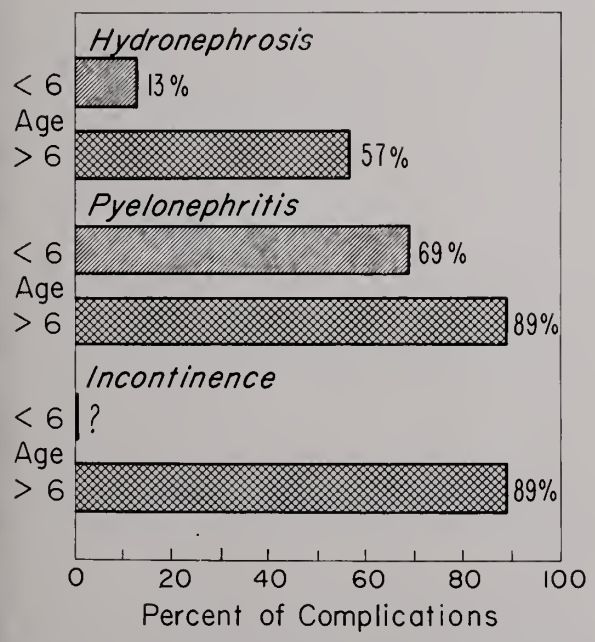


Fig. 2—This graph shows the incidence of hydronephrosis, pyleonephritis and incontinence before and after the age of six, if urinary diversion is not performed.



Fig. 3—These three x-rays show the effects of urinary obstruction and infection. Fig. 3(A) is a retrograde urogram demonstrating hydronephrosis.



Figure 3(B) is a cystogram demonstrating reflux with hydronephrosis and infection on the opposite side.

creased with age, definitive treatment should be done before age six. In addition, reflux was present in 41 percent of all children and by age 10 was always associated with hydronephrosis. (Figure 3B). Reflux is, therefore, a bad prognostic sign.

Pyelonephritis

The majority of children had a urinary tract infection. Control with antimicrobials is mandatory to prevent progressive destruction of ureteral musculature or renal parenchyma. Unfortunately, asymptomatic bacilluria often persisted even after urinary diversion, but clinical episodes of acute sepsis were rare after diversion.

Incontinence

Only four of 37 older children were continent; one of these did not have a neurogenic bladder. The rest needed urinary diversion for incontinence alone, although five males have been maintained with temporary success by an external collecting device.

Nearly all children require urinary diversion for either urinary incontinence or later for progressive hydronephrosis. To avoid missing the few that will acquire continence, surgery should be delayed until age five but should be done earlier if either hydronephrosis or refractory infection becomes a problem. During observation antimicrobial medications should be used to keep the urinary tract sterile.

*See Test Your Word Score, Page 277.



Fig. 3(C) is an intervertebral disc following urinary diversion.

The most satisfactory method of urinary tract diversion has been an ileal loop, although in three cases a loop of sigmoid colon worked nicely. Cutaneous ureterostomy was done only with severe hydronephrosis and the results were limited by the original poor status of the urinary tract (Figure 3C).

Orthopedic Problems

Back

Scoliosis, kyphosis, and lordosis are a common complication of myelomeningocele: the results of at least two different etiological factors: congenital defects and paralysis. Approximately 20 percent of the patients have hemivertebra, transitional vertebra, and various fusion defects which result in scoliosis. Because of the paralysis, an additional 35 to 40 percent of the patients have scoliosis or kyphosis. Lordosis is usually associated with high lumbar lesions which have hip flexors but no other musculature present. Curves secondary to congenital anomalies are manifested early in life and are extremely variable in expression. The paralytic curves may be very minimal through the early years but progress at an alarming rate as the patient approaches adolescence (Figure 4). Children with this degree of collapsing scoliosis of necessity use their upper extremities to support themselves and are therefore unable to perform other useful activities while sitting.

Gillette State Hospital has been a pioneer in the treatment of scoliosis with the Milwaukee brace and ideally this could be used for myelomeningocele patients. However, most of these children have anesthetic skin which makes it impossible for them to appreciate pressure from the brace. Also there is no orthotic* device which will effectively control lumbar lordosis. As a result, the place of bracing is quite limited. Ultimately these patients must have internal stabilization of their spine to allow them the full range of ambulation compatible with their neurological level; the specific method of treatment depends upon the area of the curve and its severity. All the

modalities of treatment utilized in other scoliosis patients have application here: the severe cases may need a course of halo-femoral traction prior to surgery; Harrington rods may be utilized to provide correction and internal stabilization, and in some selected patients interbody fusion is also indicated.

Hips

Like spine problems, hip problems are related to the level of the lesion. In myelomeningoceles above the level of T12, the hips are flaccid; there is no muscle imbalance about the hips and dislocation is very infrequent. The most common complication is contracture of the hip resulting from poor positioning. These contractures may be treated with physical therapy but occasionally require surgical releases; they are better prevented than treated.

In lesions of the lumbar area of the cord, the hip flexors and adductors are active but the abductors and extensors are flaccid, resulting in a flexed, adducted hip dislocated posteriorly. Dislocation is thus due to imbalance of muscle power acting about the hip and is not amenable to treatment normally used for congenital dislocation of the hip. Recurrent dislocation can be anticipated because of the persistent muscle imbalance and contractures. The current method of treatment consists of open reduction of the hip and transfer of the iliopsoas tendon through a window in the iliac crest, attaching it posteriorly and laterally into the greater trochanter (Sharrard, 1964), thus providing abduction and extension as well as removal of a deforming force. The expected result is a stable hip which will not redislocate, on which the child can ambulate.

In lesions of the sacral area the hips are stable. The abductors are innervated and some innervation is present to the extensors. Treatment is directed towards strengthening the abductors and extensors and toward gait pattern training.

Feet

In lesions above L4 the feet are totally flaccid. As a result, one might expect these children to be relatively free of foot deformity, but this is not the case. Nearly 40 percent of myelomeningocele patients have associated congenital talipes equinovarus (clubfeet). The

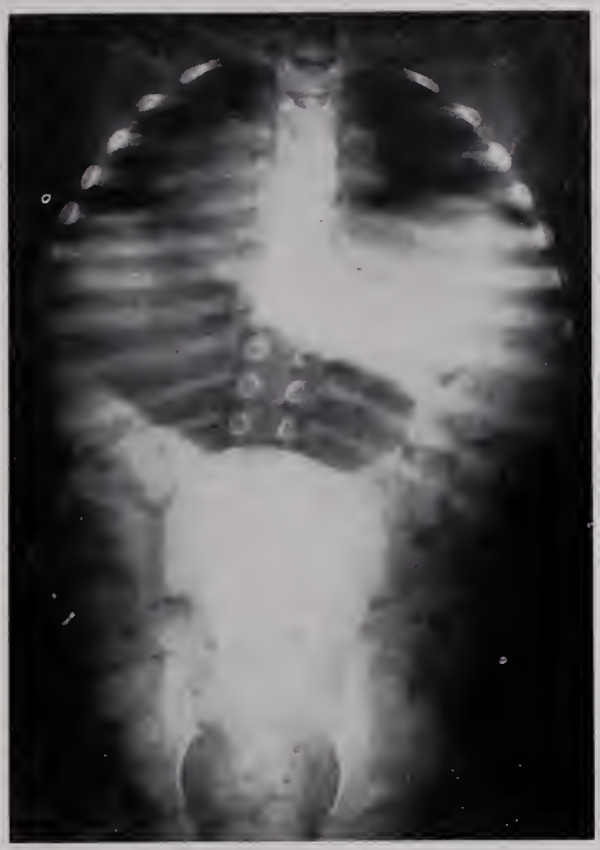


Fig. 4(A)—These x-rays show the progression seen in high lumbar or low thoracic lesions. Figure 4(A) above was taken at age nine.



Fig. 4(B)—X-ray taken at age 19.

etiology of this is unknown and these feet are considerably more resistant to treatment than the ordinary clubfoot. When the L4 nerve root is spared, the anterior and posterior tibialis muscles are innervated and are unopposed by gastrocnemius or peroneal muscles. The result is a calcaneovarus foot. The deformity must be corrected by stretching or casting followed by muscle transplant to balance the foot. Lower lesions may produce imbalances between the extrinsic and intrinsic musculature of the feet, but these are not usually severe and may be handled by tendon transfer or releases. Surgery on the feet is frequently complicated by anesthetic skin which, if present, is a problem.

Pediatric Problems

A pediatrician is intimately involved with these children from birth through the teens. These children are extremely susceptible to infections, the most common being meningitis, usually associated with an unoperated or unepitheliazed sac. In several reviews of the cause of death in children with myelomeningocele, meningitis leads in the first few years of life. Cautious antibiotic management should continue until the sac is closed.

The usual problems of growth and development for any child also exist for the child with a myelomeningocele; in addition there are unique complications because of the frequent surgical procedures early in life. The fluid and electrolyte balance during this period is difficult due to the relatively large extracellular fluid compartment of infants and, therefore, the potential of dehydration needs constant care. Once past this period the inactivity results in excess weight gain which is almost inevitable. Every teenager referred to Gillette has been obese; therefore, close watch of the weight throughout is essential.

Because of the lack of innervation of the sigmoid and rectum, constipation is a universal problem with these children. The pediatrician finds himself in the role of counseling the parents in the use of the dietary regulation, stool softeners, and occasional digital removal so that rectal prolapse may be avoided.

References may be secured from the author or the reprints.

Discussion

The wide range of the problems of the myelomeningocele child requires many different disciplines in the total management of the patient. A team approach with complete cooperation between neurosurgeons, urologists, orthopedists, and pediatricians is not only appropriate but definitely indicated. The cooperation and communication must extend to physical therapy, brace shop, social service, school setting, psychologist and vocational guidance. No one person can combine all these functions; yet without the team approach one department can easily make decisions which influence other specialists without reference to the overall plan.

The complexities of treatment may seem overwhelming to the parents, the patient, and sometimes even the physician himself; therefore, the long-range view must be adopted. The first few years are spent in direct surgical intervention and structured therapy with frequent prolonged hospitalization. However, the ultimate objective is final rehabilitation to the maximal functional status consistent with the level of neurological involvement. This frequently can mean an independent life in open employment.

Summary

Myelomeningocele no longer carries the grave prognosis and institutional existence formerly associated with the disease. A reasonably active life in open employment and normal mentality are a reasonable expectation for many afflicted children. The goal can be reached only by the joint effort of neurosurgeon, urologist, orthopedic surgeon and pediatrician working together. Long-term follow-up and anticipation of potential problems cannot be overstressed.

Bon Mot

If you feel you have no faults—that makes another one.—Mark Wachs.

Retroperitoneal Fibrosis

Presenting As Acute Iliofemoral Thrombophlebitis

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SINCE THE ORIGINAL description of idiopathic retroperitoneal fibrosis by Ormond in 1948,[1] the urologic aspects of the disease have predominated in most reported cases. The findings of vascular obstruction, either arterial or venous have been unusual. For this reason, we would like to describe the following case:

Case Report

History

A 64-year-old man was admitted to Methodist Hospital, Minneapolis, on March 16, 1968, complaining of a swollen left leg which had become progressively enlarged during the previous two days. During the three weeks prior to admission he had noted intermittent cramping in the left calf when walking but otherwise had no symptoms related to the lower extremities. There had been no recent history of trauma, but he had injured his back in a fall approximately two years before and was off work for four days at that time.

Two and one-half weeks prior to admission he had developed a sharp pain in the right hip, which radiated to the back and down both legs, and was accentuated by coughing. The pain subsided after the administration of mild analgesics and disappeared in two days.

His past health had been excellent. He had not smoked for many years, and was taking no medications.

Physical Findings

Physical examination disclosed a large, moderately obese man with a blood pressure of 160/90. The lungs were normal and there were no cardiac murmurs. The abdomen was obese but otherwise negative. The genitalia were normal. The rectal examination was negative. The right leg was normal. The left leg was massively swollen with pitting edema extending to the level of the inguinal ligament. There was marked left calf tenderness, and a positive Homan's sign was present. The dorsalis pedis pulse was normal but the posterior tibial pulse was not palpable.

Laboratory Findings

Laboratory data included a hemoglobin of 13 grams per cent, with a normal white count and differential. The sedimentation rate was 24 mm. per hour. Urinalysis was negative with the exception of eight white blood cells and two hyaline casts per high power field.

The chemistry survey profile was within normal limits. The chest x-ray showed slight left ventricular cardiac enlargement, but was otherwise normal. The electrocardiogram disclosed left axis deviation.

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*Presented at the Minnesota Surgical Society Meeting, St. Paul, Nov. 1, 1968.

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‡Department of Medicine, Methodist Hospital, Minneapolis.

Progress

After a diagnosis of acute left ileofemoral thrombophlebitis, the patient was begun on a treatment regimen which included hot packs, elevation, heparinization and intravenous dextran. There was some slight decrease in the swelling of the left leg, but mild tenderness persisted in the calf and the patient had recurring bouts of left inguinal pain though he remained afebrile and there was no significant elevation in the pulse.

On April 25, the tenth day of hospitalization, he developed severe left pleuritic chest pain accompanied by mild cyanosis and dyspnea. A chest x-ray showed an infiltration in the left lower lung field (Figure 1).



Fig. 1—Posteroanterior chest x-ray showing an infiltrate in the left lower lung field.

Surgery

The surgical consultant felt that the history and findings supported the diagnosis of pulmonary embolization with infarction, despite adequate heparin administration. Because of this, as well as the failure of the thrombophlebitis to improve, inferior vena caval interruption and venous thrombectomy were recommended.

Under general anesthesia a right flank incision was made using the retroperitoneal approach to the inferior vena cava. The right spermatic vein and the right ureter above the level of the pelvic brim were tremendously dilated. Below this point the ureter was constricted as it entered an area of dense fibrosis. This suggested that we were dealing with retroperitoneal fibrosis. Further dissection identified the retroperitoneal duodenum, but nowhere were we able to identify the inferior vena cava. The aorta could be palpated but it was encased in a dense rind of fibrous tissue. Dissection in this area was difficult and bloody since there was marked venous hypertension producing numerous dilated retroperitoneal veins. We then reasoned that by passing a catheter up through the left femoral vein into the iliac venous system we could identify the point of obstruction. Therefore the left femoral vein was exposed and a Fogarty catheter was passed distally without encountering obstruction or retrieving any clots. Proximally the catheter met an obstruction 5 cm. above the inguinal ligament. The venotomy was closed and the previously made retroperitoneal incision was extended across the midline into the left lower quadrant. The left iliac vein was exposed proximal to the inguinal ligament and explored upward. Shortly above the inguinal ligament the external iliac vein was compressed by the fibrosing process. We began dissection here and, working cephalad, tried to free the vein.

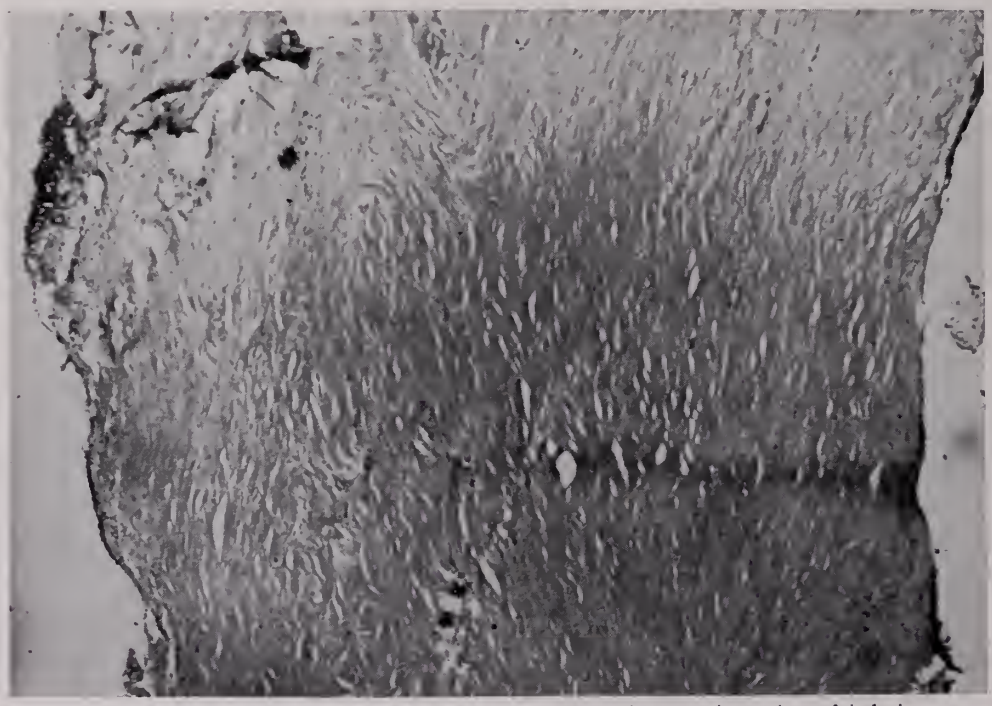


Fig. 2—Photomicrograph of tissue removed from retroperitoneum in region of inferior vena cava.

However, there was little or no cleavage plane, and on several occasions the lumen of the vein was entered. Further proximal dissection confirmed the fact that the common iliac vein was essentially obliterated. Several specimens sent for frozen section failed to reveal anything but fibrous tissue (Figure 2).

The left ureter was identified above the pelvic brim but was not dilated; therefore it was not further dissected. The right ureter was freed distally from its encasing fibrous tissue. Bleeding throughout the procedure had been profuse. As it seemed that nothing further could be done to free the obstructed venous system, the procedure was terminated.

Postoperative Course

Postoperatively, recovery was complicated by fluid retention, recurrent left pleural effusion requiring thoracentesis, hematuria and rectal bleeding. Urologic consultation was obtained. An intravenous pyelogram showed marked dilation of the right upper urinary tract, with some narrowing and delay in the passage of dye through the midportion of the ureter. The left kidney was small and there was no visualization of the left ureter (Figure 3).



Fig. 3—Intravenous pyelogram showing dilation of the right upper urinary tract.

The patient was started on steroids on April 2. A bilateral femoral venogram was done on April 11 (Figures 4 and 5) which showed the right common iliac vein to be dilated and totally obstructed at its entrance into the inferior vena cava. Since the left iliac vein was also totally obstructed, drainage from the left leg was entirely by deep collateral veins. The lumbar and azygous collaterals were tremendously dilated and the inferior vena cava was not visualized.

The patient continued to improve until April 14, when he developed abdominal pain and symptoms of an acute distal small bowel obstruction. Because of persistence of these symptoms he underwent exploratory laparotomy on the following day. Multiple dense adhesions causing distal small bowel obstruction were encountered and were lysed. A gastrostomy was done and the small bowel was decompressed using a Baker tube. Under the same anesthetic cystoscopy and right ureteral catheterization were carried out. Postoperatively, the patient had further fluid retention but this responded to intensive diuretic administration. He continued on steroids and at the time of discharge on May 3 was taking 5 mg. of prednisone three times a day. The ureteral catheter was removed on April 20. An intravenous pyelogram made on the day of dismissal showed marked improvement in excretion but residual hydronephrosis on the right.

Since discharge the patient has had only minimal swelling of the left leg and is able to ambulate without difficulty. His blood urea nitrogen has remained within normal limits.

Discussion

Idiopathic retroperitoneal fibrosis is a progressive, sclerosing, inflammatory reaction of unknown etiology, beginning in the midline of



Fig. 4—Right femoral venogram showing obstruction and dilation of the right common iliac vein and nonvisualization of the inferior vena cava.

the retroperitoneum and spreading laterally to infiltrate the surrounding structures. One might deduce that the medially placed arteries and veins would be involved at an earlier stage of the disease than the ureters which lie more laterally; however, in most instances, the findings of obstructive uropathy predominate the clinical and pathologic picture. Only 12 cases



Fig. 5—Left femoral venogram showing complete obstruction of the left external iliac vein with well developed pelvic collaterals.

of this disease have been reported[2] in which obstruction of the inferior vena cava or iliac venous systems caused swelling of the legs or edema of the scrotum or hydrocele.

Ideally, diagnosis of idiopathic retroperitoneal fibrosis should be made early, before extensive involvement of the ureters occurs. In cases of vascular occlusion, this could be done by appropriate angiographic studies. However, angiograms are not always practical, as illustrated in the foregoing case. Even when available, the venographic appearance may be nonspecific. Schaefer et al. have advocated delayed flat films of the urinary tract following angiograms to demonstrate the anatomic detail of the kidneys and ureters.

In a classic case of retroperitoneal fibrosis one will note the triad of (1) dilation of the proximal ureter and calyces* system, (2) constriction of the distal ureter and (3) medial displacement of the ureter at the level of the third and fourth lumbar vertebrae. When these findings are encountered in association with arterial or venous obstructive lesions, it is reasonable to conclude that one may be dealing with retroperitoneal fibrosis.

The treatment of choice is surgical excision of the constricting fibrous plaque. This may be difficult to accomplish, however, as illustrated by our case, especially where there is actual obliteration of the large veins and a good dissection plane is virtually impossible to maintain. Dissection in a case of aortoiliac arterial constriction was considerably easier in a case previously encountered by us.[3] Perhaps the preservation of this anatomical plane was due in part to the thicker wall of the artery or its pulsatile nature. Ureteral dissection may also be tedious and difficult. Transplantation of the liberated ureter within the abdominal cavity has been advocated by some, but this also has failed to prevent progressive ureteral obstruction in certain cases. X-ray therapy has been used but has not met with widespread acceptance. Most authorities feel that these patients should be maintained on long-term steroid therapy; this has been done in our case.

Conclusions

Idiopathic retroperitoneal fibrosis presenting as an acute left ileofemoral thrombophlebitis caused obstruction of the right ureter and complete obliteration of the inferior vena cava and left iliac veins. It was possible to release the right ureter but nothing could be done to re-

*See Test Your Word Score, Page 277.

lieve the obstructed venous system; nevertheless, swelling of the left leg relented, presumably due to establishment of new collateral channels. The patient has remained on steroids and his progress has been excellent from a urologic standpoint.

Idiopathic retroperitoneal fibrosis is rare as a cause of ileofemoral thrombophlebitis. However, this condition should be kept in mind on certain occasions and, where possible, venograms made with delayed x-ray exposures of the kidneys and ureters will aid in a preoperative diagnosis. If an early diagnosis can be made, surgical lysis of the fibrous plaque, especially in the case of venous obstruction, should be greatly facilitated and better long-term results anticipated.

Acknowledgment

Dr. Roger R. Lundblad saw this patient in urologic consultation and performed the cystoscopy and retrograde pylographic studies.

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It's the Law

Government Not Bound by Own Medicare Booklet

A claim by a Medicare beneficiary for expenses connected with his emergency hospitalization following a heart attack has been denied by the Social Security Administration on the grounds that the hospital was not a Medicare participant. A handbook of Medicare information, signed by the Social Security Commissioner, states that "in an emergency, if you are taken to a hospital that is not participating, your hospital insurance will pay for the covered services you receive." In the order rejecting the claim, it was stated that the booklet was incorrect, since nonparticipating hospitals must meet certain requirements to qualify for payments even under the emergency clause.

(News Release, Ruidoso, New Mexico, Nov. 1, 1967.)
The Citation, 16:7, January 15, 1968.

19th Century Failures

Andrew Jackson

Another sickly but durable patient was Andrew Jackson. Through military and political campaigns and two terms as president, he suffered lung abscess, cough, fevers, pulmonary hemorrhages, osteomyelitis, and periodic diarrhea. He carried a duelist's bullet in his chest for nearly forty of his seventy-eight years, and another bullet in his elbow which a surgeon removed after sixteen years. His favorite medication was lead acetate, which he used as an eyewash, poured into wounds for quick healing, and drank for intestinal cramps.*

*The Patient's Progress, Edited by Marti-Ibanez, 1962.

Editor's Note: He probably had developed a reliance syndrome: using lead acetate for almost anything. No wonder he had intestinal cramps!

The Ailments of Men in History

Samuel Pepys and His Stone

Mr. Pepys suffered from stone in the bladder before he began to keep a dairy.

Cutting for the stone was one of the earliest surgical operations. In ancient days it was first done in India, and the glad news that stones could be successfully removed from the living body filtered through to the Greeks some centuries before Christ.

By Pepys' time Marianus Sanctus had lived—yes, so greatly was he venerated that they called him "Sanctus." He it was, in Italy in 1524, who invented the apparatus major, which made the operation a little less barbarous than that of the Greeks. This God-sent apparatus consisted mainly of a grooved staff to be shoved into the bladder and a series of forceps. You cut on to the staff as the first step of the operation; it was believed that if you cut in the middle line in the raphe the wound would never heal, owing to the callosity of the part; moreover, if you carried your incision too far back you would cause fatal haemorrhage from the inferior haemorrhoidal veins. Having, then, made your incision well to the right or left, you exposed the urethra, made a good big hole in that pipe, and inserted a fine able pair of tongs, with which you seized hold of the stone and crushed it if you could, pulling it out in bits; or if the stone were hard, and you had preternaturally long fingers, you might even get it out on a finger-tip. It was always considered the mark of a wise surgeon to carry a spare stone with him in his waistcoat pocket, so that the patient might at least have a product of the chase to see if the surgeon should find his normal efforts unrewarded.

This would be the operation that was performed on Mr. Pepys. One unpleasant result was the fact that whenever he crossed his legs carelessly he became afflicted with a mild epididymitis—he describes it much less politely himself, doubtless in wrath. His little failing in this respect must have been a source of innocent merriment to the many friends who were in the secret.

When he died, an old man, in 1703, they performed a post-mortem examination on his body, suspecting that his kidneys were at fault, and in the left kidney found a nest of no less than seven stones, which must have been silently growing in the calyces for unnumbered years.*

*C. MacLaurin: Post Mortems of Mere Mortals, 1925.

Editor's Note: The God-sent apparatus described as a grooved staff must have been a bistoury projected through the perineum on into the posterior urethra. Without anesthesia? Ouch! What worse than that could the Greeks have dreamed up.

The School of Salerno

When To Eat

To keepe good dyet, you should never feed
Until you finde your stomacke cleane and void
Of former eaten meate, for they do breed
Repletion, and will cause you soone be cloid,
None other rule but appetite should need,
When from your mouth a moysture cleare doth void.*

*Regimen Sanitatis Salerni.

Editor's Note: The School says: Don't eat unless your stomach is empty; and don't eat unless your mouth waters.

Agnogenic Myeloid Metaplasia

Its Current Management

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AGNOGENIC† MYELOID METAPLASIA is a myeloproliferative disorder closely associated with polycythemia vera, chronic granulocytic leukemia, and hemorrhagic thrombocythemia. At the Mayo Clinic we see 35 new cases of agnogenic myeloid metaplasia each year; the disease thus approximates the frequency of chronic granulocytic leukemia in our practice.

Agnogenic myeloid metaplasia may arise *de novo*† or from another myeloproliferative state.[1] In our experience, polycythemia vera preceded agnogenic myeloid metaplasia in 25% of cases.[2] About 5% of patients have had previous chronic granulocytic leukemia, and rarely does hemorrhagic thrombocythemia evolve into agnogenic myeloid metaplasia.[3]

Clinical Features

Most often agnogenic myeloid metaplasia develops in patients who are between 50 and 60 years old. Males and females are equally affected. About 50% are symptomatic when first seen. Symptoms result either from anemia or from mechanical discomfort of the enlarged spleen. On examination, the outstanding feature in all patients is splenomegaly. Splenic enlargement may be to the level of the umbilicus, or the spleen may fill the entire left side of the abdomen. Modest pallor secondary to anemia is noted in 70% of symptomatic patients, and purpura or ecchymoses as a result of thrombopenia may be observed in 15% or less.

Laboratory Findings

Anemia observed in 70% of symptomatic patients is of the normocytic and normochromic type. Thirty percent of the patients have leukopenia, 50% have between 5,000 and 10,000 leukocytes/cu mm, and less than 15% have counts in excess of 30,000. Thrombopenia occurs in about 15% of patients.

The peripheral blood smears usually contain certain features. Red cells show characteristic

*Mayo Clinic and Mayo Foundation: Section of Medicine.
†See Test Your Word Score, Page 277.

teardrop poikilocytosis. Myeloid immaturity and normoblasts are observed in 90% of patients, and megakaryocyte fragments are noted in 50%. Other features on the smear may include basophilia and giant platelets.

Bone-marrow aspiration may be difficult to perform. Ninety percent of patients will have marrow smears that are hypocellular and marrow sections that reveal extensive fibrosis. It is notable, however, that 10% of patients may have normocellular or hypercellular smears, and fibrosis is not seen on section.

Diagnosis

The diagnosis of agnogenic myeloid metaplasia is based on: (1) the presence of splenomegaly, (2) a characteristic peripheral blood smear that demonstrates teardrop poikilocytosis, leukoerythroblastosis (myeloid immaturity and normoblasts), megakaryocytic fragments, basophilia, and giant platelets, and (3) bone-marrow smears that are hypocellular and marrow sections that are fibrotic.

Differentiation from polycythemia vera should not be difficult because in agnogenic myeloid metaplasia there is no increase in the absolute mass of the circulating red cells. Differentiation from chronic granulocytic leukemia also can be made because, in the latter syndrome, anemia is not a feature, the peripheral leukocyte count is in excess of 100,000/cu mm, and the marrow is always hypercellular, with left-shifted granulocytic hyperplasia. Also the Philadelphia chromosome is a constant feature of chronic granulocytic leukemia. Hemorrhagic thrombocythemia should present no difficulty in the differentiation because the anemia of this syndrome is hypochromic; platelet counts are in excess of 1,000,000/cu mm, and the marrow is peppered with platelets in association with megakaryocytic hyperplasia.

Management

To provide effective management for agnogenic myeloid metaplasia, knowledge of the natural history of this disorder is important.[2] About 50% of patients with agnogenic myeloid metaplasia are *asymptomatic* when first seen, and 80% of these will manifest no significant deterioration from their disease. The probability that these patients will survive is 70% of normal. Causes of death in these patients are primarily due to degenerative vascular disease.[4] Patients with asymptomatic agnogenic myeloid metaplasia require no therapy. Periodic follow-up examinations at six-month intervals are indicated to determine any change in the hematologic status.

About 50% of patients with agnogenic myeloid metaplasia are *symptomatic* when first seen, and the two major symptoms are anemia and mechanical discomfort from the enlarged spleen.

The anemia of agnogenic myeloid metaplasia is usually due to one of two mechanisms: first, progressive bone-marrow failure with fibrosis leads to ineffective erythropoiesis, and second, to a hemolytic mechanism in association with hypersplenism.

To adequately control the anemia in agnogenic myeloid metaplasia, the mechanism of the anemia should be determined. If bone-marrow failure is the prime factor, androgens are the therapy of choice. Testosterone enanthate (Delatestryl), in weekly doses of 400 to 600 mg given intramuscularly, or fluoxymesterone (Halotestin), 10 mg three times a day given orally, is worth a trial. If hemolysis is the major cause of anemia, adrenal steroids are indicated. Prednisone in doses of 40 to 60 mg a day is the treatment of choice.

The treatment of anemia should be undertaken when hemoglobin levels decrease to below 10.0 gm. Occasionally judiciously infusing packed red cells may help when combined with drugs to control anemia.

In some patients, severe hemolytic anemia may occur, and infusions and adrenal steroids may not be effective in controlling it. Also, combined tag studies with radioactive chromium and iron should be performed and, if splenic sequestration is excessive, splenectomy is indicated. Seventy percent of our patients with severe hemolysis and hypersplenism respond well to splenectomy.[5] Splenectomy should never be undertaken in patients with agnogenic myeloid metaplasia unless special coagulation studies are done. If patients are free of platelet abnormalities, that is, if there is no decrease in platelet factor III or platelet

adhesiveness, successful surgery can be anticipated. If splenectomy is highly desirable, despite the presence of coagulation abnormalities, careful preparation of such patients also may be an aid to a successful surgical outcome.

The other major symptom of agnogenic myeloid metaplasia results from the mechanical discomfort from massive splenomegaly. Patients who have extreme discomfort are candidates for splenectomy. Patients so treated for massive splenomegaly have a 50% chance of a good result.[5] Patients treated with busulfan (Myleran) for massive splenomegaly have responded poorly,[2] and radiation therapy has led to deterioration in the basic disease.[2] Radiation, however, may be useful in patients who have severe pain secondary to acute infarction of capsular areas of the spleen. Patients with minimal distress from splenic enlargement should be observed, without any specific therapy. However, if extreme discomfort accompanies massive splenomegaly, treatment is indicated, and splenectomy is the treatment of choice.

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Evolution of an Editor

My editorship of THE JOURNAL could be described as a constant striving for fundamental principles involved in editing. Notwithstanding the argument that the progress of medical sciences allows for plenty of time in bringing information to physicians and the public, I was stimulated to shorten to the minimum the interval between the development of information and its publication.

I abominated unnecessary words, tables, charts, and pictures. I opposed the use of flowery, fanciful diction. My primary objective was a succinct, clear statement of fact. I emphasized that the summary of an article should summarize the factual material; the conclusions would permit hypotheses and interpretation and even prediction, but these must not go beyond the facts.

Controversy is the enzyme that sets off an explosion of interest and excitement. I do not believe in the publication of immense bibliographies as parts of an article, but I value bibliography as it must be available to other workers in the field.

Many a battle arose when the proofs reached the authors, over the editing, rewriting, and correcting of articles accepted for publication. One of the most important of these involved Dr. William Sydney Thayer, eminent professor of medicine at Johns Hopkins, who began his presidential address with the word " 'Tis." I suggested in a scientific article this might just as well be "It is," although I dislike "It is" just about as much as I dislike " 'Tis." He disliked my criticism; we compromised by printing the words "It is" in THE JOURNAL and " 'Tis" in the reprints.*

*Morris Fishbein, M.D.: An Autobiography, 1969.

Literary Men Who Studied Medicine

Certified Apothecary John Keats

"In disease medical men guess; if they cannot ascertain a disease they call it nervous." This succinct and wry statement was John Keats' summation of medicine in England in the 19th century.

For a fee of one pound, two shillings 20-year-old Keats was admitted to Guy's Hospital in London as a "surgeon's pupil." He must have proved an apt if not precocious pupil, for after only six months of a one-year course he advanced to status of "dresser," under the aegis of one Dr. Lucas who was described as "a tall ungainly, awkward man, with stooping shoulders and a shuffling walk, as deaf as a post, not overburdened with brains . . . His surgical acquirements were very small, his operations generally badly performed, and accompanied with much bungling, if not worse."

For anyone familiar with Keats as a poet it is hard to visualize him as one of the host of student observers, indecorously rushing into and packing the operating room each Friday: Guy's at noon and St. Thomas' at one o'clock, jostling and shoving one another and shouting "Heads, heads!" at those in front who obstructed their view of what the terrified unanesthetized patient was undergoing on the dirty, blood-stained table.

After the surgeon had seen to the first few dressings, accompanied on his rounds by the students, the dressers took over on the wards—doing their inadequate utmost to save lives, but powerless against infection: that all too frequent, insidious, and usually fatal aftermath of total disregard for asepsis.

As a dresser Keats had to take periodic and responsible charge of the surgical ward, on 24-hour call, unremunerated for his services, with each Thursday devoted to hordes of outpatients: dressing injuries, pulling teeth, doing venesections, and taxing his discretion and judgment as to which patients, if any, required the more skilled evaluation and service of the head-surgeon.

While at St. Guy's Keats became familiarized with the conventional subjects of surgery, anatomy, chemistry, midwifery, and also materia medica, the "classroom" for which was an herb garden at Chelsea, which must have constituted a fresh and verdant haven for the sensitive, nature-loving young man—in contrast with the drab lecture halls and laboratories.

But no such welcome refuge the dissecting-room, which must have revolted an even less fastidious temperament than Keats' by its shrouded, ghoulish "resurrection-men" stealing in furtively at night with their macabre bundles of "anonymous" corpses required by the anatomy courses.

According to The London Medical Repository John Keats became a Certified Apothecary in 1816 when not quite 21 years old. However, proficiency and humanitarianism alone were not enough to fire young Keats to a permanent career in medicine. Perhaps a catalyst was needed: a dynamic mentor like Sir Astley Cooper, instead of Lucas. But perhaps not! The poet in Keats could not be gainsaid.

Keats' heart was elsewhere—in that exalted and compelling realm of beauty and truth* with its sensuous imagery for which only a poet has vision and that cannot be denied without crucial personality violation. Suspecting correctly that he was basically unfit for a medical career, Keats decided to abandon medicine to write poetry. Later he wrote these revealing words to a friend: "My last operation was the opening of a man's temporal artery. I did it with the utmost nicety, but reflecting on what passed through my mind at the time, my dexterity seemed a miracle, and I never took up the lancet again." And after his renunciation, Keats said most prophetically: "I think I shall be among the English poets after my death." And he is! So when London lost a doctor, the world gained an immortal poet.

*"Beauty is truth, truth beauty,—that is all Ye know on earth, and all ye need to know."

Intra-Aortic Balloon Pumping*

Effect in Sheep with a Ligated Coronary Artery

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INTRA-AORTIC BALLOON pumping was conceived in 1961[1,2] as a modification of diastolic augmentation by an extracorporeal pump.[3] Many investigators agree that it is a simple method for mechanical assistance to the failing circulation;[4,5] although a quantitative estimate of the mechanical assistance needed in each particular case is not yet available.[6,7,8] Recently Brown et al.[9] demonstrated significantly increased left circumflex coronary artery flow during diastolic pumping with a double balloon following ligation of the anterior descending coronary artery in dogs. Indirect support may be derived from the excellent results obtained in dogs with another form of counterpulsation by Rosensweig and Chatterjee;[10] they report that counterpulsation in dogs with cardiogenic shock restored oxidative myocardial metabolism, reduced myocardial irritability, improved cardiac function, and prevented myocardial infarction. Kantrowitz et al.[11] have already used the intra-aortic balloon pumping in 15 patients who were in profound cardiogenic shock when aortic balloon pumping was started as a last resort. Of the nine patients that eventually died, six improved temporarily. Their blood pressures were improved, their urinary outputs were restored, and the common picture of shock was reversed. Six of the 15 patients recovered.

We want to report: (a) technical improvement, (b) effectiveness of the method in sheep following coronary artery ligation, and (c) limitations of the method as seen during these experiments.

Material and Method

Ten sheep (60-80 kg. body weight) were anesthetized with a continuous intravenous drip of sodium methohexital. Following a left thoracotomy, an ultrasonic and an electromagnetic flowmeter probe were placed around the root of the aorta and the upper part of the descending aorta respectively. A polyethylene catheter was inserted into the left atrium and was used for pressure monitoring.

*See editorial page 273.

A ligature was placed around the anterior descending branch of the left coronary artery and left in place for subsequent ligation. The femoral artery and the carotid or internal mammary artery were also cannulated so that pressures proximal and distal to the balloon could be monitored at the arch of the aorta and the abdominal aorta.

The balloon was inserted through the femoral artery. In some animals the small size of this artery made it necessary to insert the balloon through the carotid artery.

In four animals a left ventricular bypass was also established. A cannula was inserted into the left atrium and was connected to an air pressure pump which pulsed the blood to another cannula sutured to the descending aorta.

The electrocardiogram of the animal was also recorded.

The equipment used to drive the balloon consisted of an R-wave detector,[12] a Cordis programmer regulating the delay from the R-wave signal of the electrocardiogram and the duration of balloon inflation, and a solenoid* air-pressure valve. Thus the pumping was initiated by the R-wave of the electrocardiogram.

Modifications in the Equipment

An R-wave detector is used to provide reliable selection of the R-wave for the initiation of each inflation of the balloon. In this instrument the electric impulses from two limbs of the animal are passed through a bandpass filter which rejects unwanted high frequency and low frequency signals. The signals are then fed to a window circuit which rejects signals with amplitudes that are too high or too low. In the next stage of the circuit signals of short duration are eliminated. Thus the R-wave component is selectively retained while all electrical signals from noise and other components of the QRS wave complex are rejected.

No vacuum pump is used to evacuate the balloon (Figure 1). Instead, the safety chamber connected to the balloon is now made of a heavy rubber tube of larger capacity; its elasticity provides ample suction for the evacuation of CO_2 from the balloon. Part of the CO_2 in the closed safety chamber space is evacuated with a syringe at the beginning of the pumping to achieve the desired partial collapse of the rubber tube and total collapse of the balloon. Doubt expressed by other workers that the evacuation may not be rapid enough appears to be unfounded. The delay between the electrical signal of the programmer and the air pressure in the balloon is measured for different inflation durations (Figure 2), and it is not neecssary to replace the CO_2, as we originally advocated, with helium. CO_2 is safer in case of a leak or rupture of the balloon.

A small "slave" balloon is added to the manifold between the intra-aortic balloon and the safety chamber to indicate the activity of the intra-aortic balloon. Made thinner, this small balloon presents a further safety factor in case of unexpectedly high pressure, as it will break.

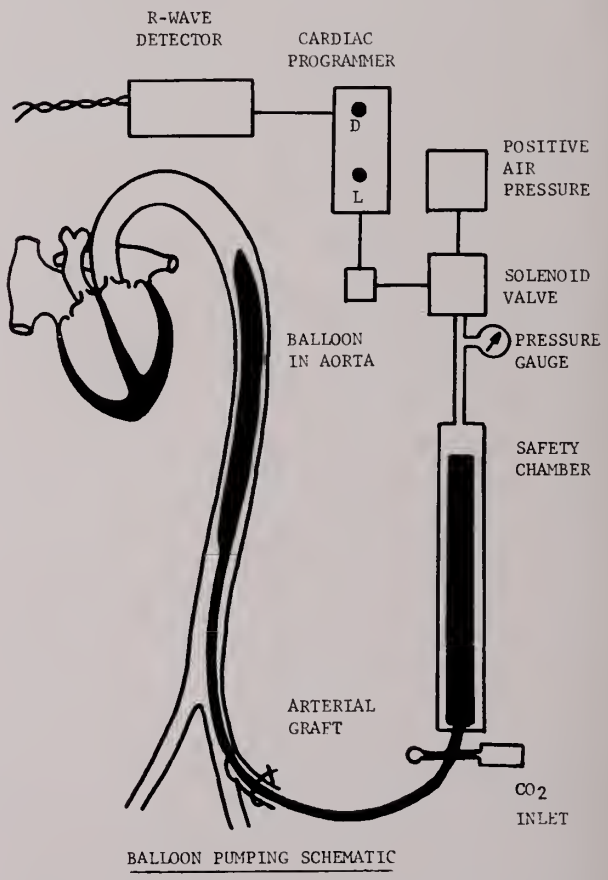


Fig. 1—Diagram of the intra-aortic balloon-pumping setup. The balloon is inserted through a femoral artery. A: Aorta; ECG: Electrocardiographic leads; RWD: R-wave discriminator; D: Delay regulating device; R: Relay; S.V.: Three way solenoid valve; P.P.: Air Pressure pump; I.: A-2 pressure gauge; L: duration; S: Safety balloon; P.T.: Pressure transducer; and S.C.: Safety chamber filled with CO_2.

*See Test Your Word Score, Page 277.

The polyethylene catheter with small side holes for inflation of the balloon is modified. The catheter now ends as soon as it enters the balloon and a stainless steel wire is threaded through to the tip of the polyurethane balloon. This wire has a drop of silver solder on its tip to prevent perforation of the balloon and to serve as a marker on the röntgenogram.

Balloons are made 30 to 40 cm. long and 1 to 1.4 cm. in diameter when inflated. We continue to use polyurethane VC* as it is stronger than any other suitable material known to us. During the relatively short period in the body, it does not deteriorate.

Procedure

The experimental procedure consisted of monitoring flows, pressures, and electrocardiogram before and during pumping, with various delays and inflation durations. The coronary artery was then ligated and, as soon as the arterial blood pressures and flows were reduced, pumping was initiated. The pumping was stopped and started several times.

In experiments with a concomitant left heart bypass, the bypass was alternated with the balloon pumping. Combination of the two was also tested.

The delay between the electrical signal from the programmer and the air pressure in the balloon did not exceed 50 msec. (Figure 2) for any duration of balloon inflation. As may be seen from the tracings, evacuation of the balloon was possible in approximately 50 msec. Since we used sheep, we inserted balloons of a size suitable for adult men, i.e., 30 to 40 cm. Even at heart rates of 160/min. the balloon could be inflated after every heart beat.

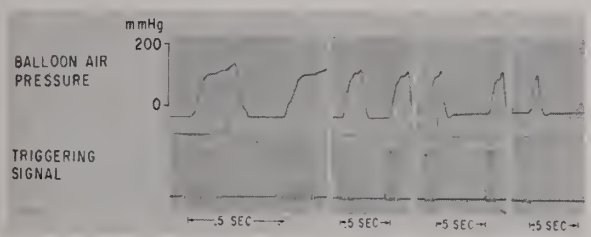


Fig. 2—Simultaneous recording of the electrical signal output of the relay (between the programmer and solenoid valve) and the air pressure in the balloon. For long duration signals the delay is approximately 50 msec.

*Estane, B. F. Goodrich.

Results

Intra-aortic balloon pumping lowered the left ventricular end diastolic pressure (Figure 3).

Blood Pressure

The aortic end diastolic pressure was reduced during pumping (Figure 3).

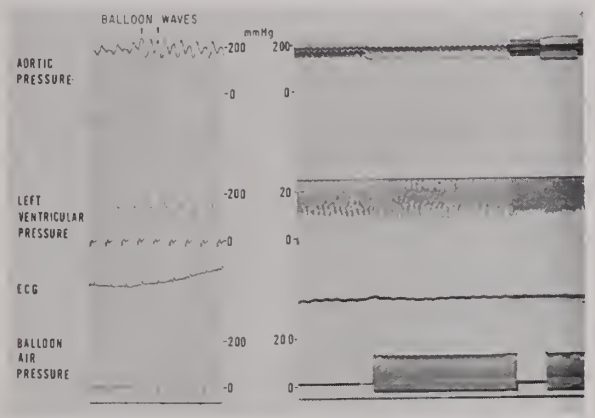


Fig. 3—Sheep experiment. Pressure waves produced by the balloon are clearly demonstrated in the aortic pressure tracing. During balloon pumping, indicated by the balloon air-pressure tracing, the aortic end diastolic and the left ventricular end diastolic pressure are lower than when the pump is off.

Actually, three waves could be seen during pumping; one corresponded to the flow produced by the contraction of the heart and one to the balloon inflation; a third followed the balloon wave in an opposite direction. This could be demonstrated better by changing the delay (Figure 4).

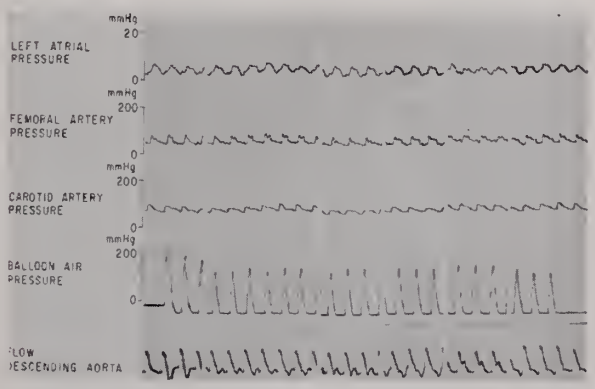


Fig. 4—Sheep experiment. The delay between R-wave and balloon inflation was varied. A diastolic wave is recorded on the flow tracing from the beginning of the descending aorta above the balloon. This is either positive or negative or biphasic according to the delay between R-wave and balloon inflation. The negative wave indicates flow toward the ascending aorta. The positive wave indicates flow toward the abdominal aorta.

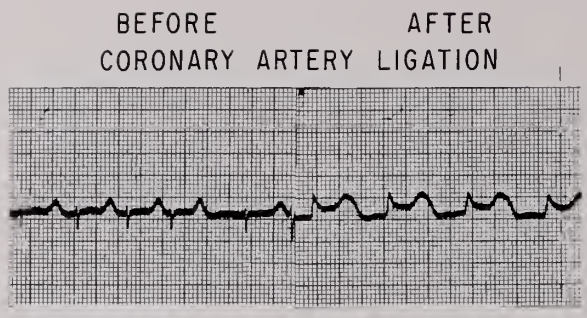


Fig. 5—Electrocardiogram changes indicating acute ischemia (S-T segment elevation) following ligation of the anterior coronary artery (lead I).

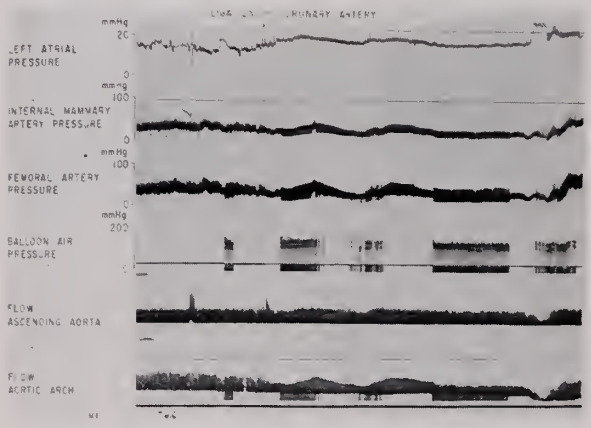


Fig. 6—Ligation of the anterior coronary artery reduces aortic flow and arterial pressures. Balloon pumping corrects the situation in three successive instances. Note the effect during the last pumping period, when flow was extremely reduced. The reaction to pumping is obvious on both flow and pressure. Flow in the ascending aorta is recorded with an ultrasonic flowmeter* while the aortic arch flow was measured with an electromagnetic flowmeter (bidirectional).

*Recording flow in either direction as positive.

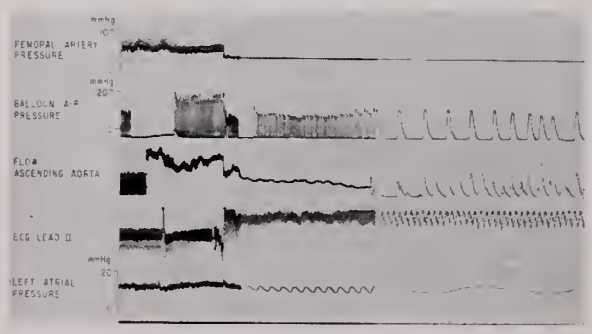


Fig. 7—Ligation of the anterior coronary artery at the site of the arrow reduces average aortic flow. Balloon pumping improves aortic flow. Reducing pumping pressure is followed by ventricular flutter. Balloon pumping becomes irregular during ventricular flutter.

Following coronary artery ligation (Figure 5) balloon pumping improved flow and pressure (Figure 6). It did not always lower the left atrial pressure, nor did it always prevent the occurrence of ventricular fibrillation. In one instance ventricular tachycardia followed immediately upon reduction of the balloon pressure (Figure 7). In three experiments the beneficial effect was repeatedly demonstrated by switching the pump on and off. In these experiments final switching off of the pump meant the death of the animal.

Flow

The effects of balloon pumping were observed in three experiments with the heart in atrial fibrillation with high ventricular rate. The effects of pumping were then similar to those of asynchronous pumping (Figure 8).

The effects of left heart bypass, tested before ligation of the artery, were more pronounced than the effects of balloon pumping, as far as pressure and flow changes were concerned (Figure 9). Simultaneous left heart bypass and balloon pumping had additive effects on pressure and flow tracings.

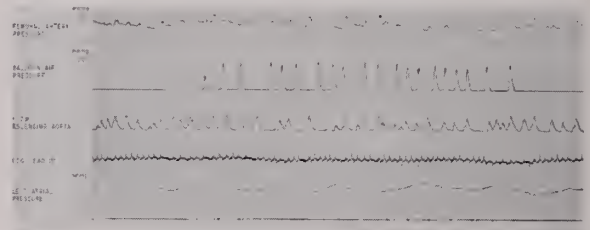


Fig. 8—Balloon pumping during atrial fibrillation. Note the irregular air pressure waves having no constant effect on the aortic flow tracing.

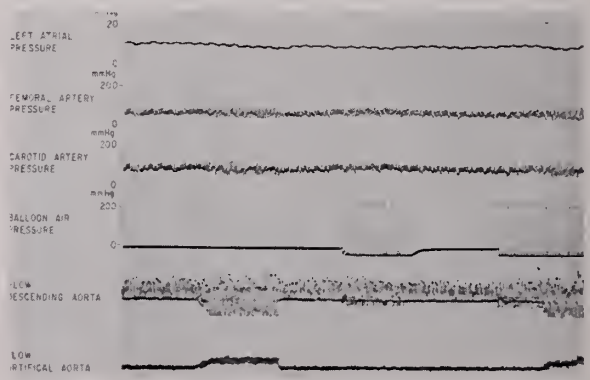


Fig. 9—Left ventricular bypass (indicated by flow waves in the artificial aorta) of approximately 1.1 L/min. is producing changes in the pattern of the aortic flow tracing. Balloon pumping (indicated by air pressure tracing) is causing less change. Tracings were obtained before coronary artery ligation.

Discussion

It is fallacious to expect beneficial effects from any form of cardiac assist unless the heart is in failure. Following ligation of the left anterior descending coronary artery in sheep, intra-aortic balloon pumping appears to have a beneficial effect in reversing the falling cardiac output and systemic pressures. This is in accordance with Kantrowitz's[11] observations in human beings and Gott's[12] findings in dogs. The beneficial effects, even in these short-term experiments, were seen to persist for a short time after pumping was stopped.

The effects of left heart bypass were more pronounced than those of the balloon pumping. However, the balloon pumping can be easily used when a thoracotomy for the installation of the left heart bypass may be inadvisable. Furthermore, it is not yet clear whether vigorous pumping by the left heart bypass is indeed beneficial for the welfare of the myocardium.

Balloon pumping cannot be used at very high heart rates. A line delay of 50 to 100 msec., plus 200 msec. for optimal inflation duration, limits its application to rates with a cycle length of over 300 to 400 msec. In cases with a shorter cycle length, pumping can be applied only after the rate has been slowed down with synchronous or paired pacing of the heart.

Another limitation exists in the application of balloon pumping during atrial fibrillation with fast ventricular response. The location of the balloon action, even with synchronous driving, is then uncertain, since the next cycle may be of quite different length. In slow-rate arrhythmias, balloon pumping may be used although some "beats" may be less than optimally positioned.

Improvements of the technique have helped to reduce noise interference in triggering the pump. Use of a heavy rubber tube safety chamber with partial vacuum has helped to reduce the deflation time. Eliminating the polyethylene multiple-hole catheter has helped to reduce the problems discussed by Laird et al.[13] Possible clogging or air-ionizing through the small holes and reduction or flow along the line may also be avoided by using a single opening. The "slave" balloon presents an additional safety device, and the metal wire with the solder tip helps to position the balloon in the aorta under x-ray control.

Finally, insertion of the balloon may in some instances present a problem. It may be impossible or dangerous in patients with severe atherosclerosis of the aortic bifurcation and iliofemoral arteries.

The use of a double balloon, as advocated by Brown and co-workers,[9] for dog and man does not seem to offer an advantage for sheep since the anatomy of the aortic arch is so different.

Summary

Intra-aortic balloon pumping presents a simple method for mechanical assistance to the failing circulation.

Experiments in sheep following ligation of the left anterior descending coronary artery demonstrate a beneficial effect of balloon pumping, consisting of increasing aortic blood flow and pressure.

Limitations of balloon pumping application refer to extremely fast heart rates (over 160/min.) and atrial fibrillation with fast ventricular response.

Use of the Gebben R-wave detector has contributed to reduced noise interference of the triggering circuit and to safer pumping. Construction modifications have led to better inflation and faster deflation of the balloon.

Addendum

Clinical evidence after this paper was written indicates that, indeed in many patients with cardiogenic shock, the blood flow and arterial pressure can be restored by intra-aortic balloon pumping. Ultimate recovery depends on the extent of the damage and is inversely proportional to time elapsed after the initial infarct.

For deep heart failure with threatening arrest, we are introducing closed-chest transarterial left ventricular bypass.[15] It will sustain the circulation even in the presence of ventricular fibrillation. It requires one cutdown on the axillary artery for introduction of a thin-walled catheter which is moved retrograde into the left ventricle and a second cutdown on a femoral artery. Blood sucked from the failing left ventricle is pumped back via the femoral artery.

References may be secured from the author or the reprints.

The Religion of a Doctor *

Sir Thomas Browne

"I hold there is a general beauty in the works of God, and therefore no deformity in any kind or species of creature whatsoever. I cannot tell by what Logick we call a Toad, a Bear, or an Elephant ugly; they being created in those outward shapes and figures which best express the actions of their inward forms."

"How America abounded with Beasts of prey and noxious Animals, yet contained not in it that necessary Creature, a Horse, is very strange."

"Those strange and mystical transmigrations that I have observed in Silkworms, turned my Philosophy into Divinity."

And finally, in his capacity as physician: "For the World, I count it not an Inn, but an Hospital; and a place not to live, but to dye in."

"Men that look no farther than their outsides, think health an appurtenance† unto life, and quarrel with their constitutions for being sick; but I, that have examined the parts of man, and know upon what tender filaments that Fabrick hangs, do wonder that we are not always so; and, considering the thousand doors that lead to death, do thank my God that we can die but once."

Browne, though a doctor, accepted Alchemy and Astrology; he declared that he himself was born under the baleful sign of Scorpio, governed by the sinister planet Saturn. Yet his life failed to demonstrate any such celestially malevolent influences.

To Browne's everlasting discredit, especially as a physician, was his belief in witches. "For my part, I have ever believed and do now know, that there are Witches." And did not Scripture charge: Suffer not a witch to live? Largely on Browne's professional court testimony that several children were bewitched, two innocent women, unjustly suspected of being witches, were convicted and executed.

Religio Medici proposes friendship to be the highest human value. "I love my friend before my self, and yet methinks I do not love him enough. When I am from him, I am dead till I be with him: when I am with him, I am not satisfied, but would be still nearer him . . . I hope I do not break the fifth Commandment,‡ if I conceive I may love my friend before the nearest of my blood, even those to whom I owe the principles of life. I never yet cast a true affection on a woman; but I have loved my friend as I do virtue, my soul, my God."

"The whole World was made for man, but the twelfth part of man for woman: Man is the whole World, and the Breath of God; Woman the Rib and crooked piece of Man. I could be content that we might procreate like trees, without conjunction, or that there were any way to perpetuate the World without this trivial and vulgar way of union: it is the foolishest act a wise man commits in all his life; nor is there any thing that will more deject his cool'd imagination, when he shall consider what an odd and unworthy piece of folly he hath committed.

For his classic, Religio Medici, Browne's niche in great World literature is secure—not because he wrote as a doctor, not because he offered to a world in transition a better operative philosophy, but because in his uniquely personal interpretation of the Scriptures he furnished a self-revelation, written in an inimitably delightful style and still captivatingly fresh after more than 300 years.

Editor's Note: Poor Sir Thomas! He probably had not heard of the aphorism about the birds and the bees and the apple trees. Perhaps Browne's value system underwent revision for, at the age of 36, he married a young woman of 20, sired numerous offspring, and became a devoted husband and father.

*See The Religion of a Doctor. Minnesota Med 53:134, 1970.
†See Test Your Word Score, Page 277.
‡Honour thy father and thy mother.



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Non-nursing mothers may begin Ovulen-21 immediotely after delivery, on the doy of deporture from the hospital or at the first postpartum visit, as desired. It is recommended thot nursing mothers begin Ovulen-21 four weeks after delivery.

A smoll froction of the hormonol ogents in oral contraceptive pills hos been identified in the milk of mothers receiving these drugs. The long-ronge effect on the nursing infant cannot be determined ot this time.

Actions—Ovulen acts to prevent ovulation by inhibiting the output of gonadotropins from the pituitary gland. Ovulen depresses the output of both the follicle-stimulating hormone (FSH) and the lutenizing hormone (LH).

Special note: Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. Both types provide almost completely effective contraception.

An increased risk of thromboembolic disease associated with the use of hormonal contraceptives has now been shown in studies in both Great Britain and the United States. Other risks, such as those of elevated blood pressure, liver disease and reduced tolerance to carbohydrates, have not been quantitated with precision.

Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency of some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can be neither affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

Indication—Ovulen is indicated for oral contraception.

Contraindications—Patients with thrombophlebitis, thromboembolic disorders, cerebral apoplexy or a past history of these conditions, markedly impaired liver function, known or suspected carcinoma of the breast, known or suspected estrogen-dependent neoplasia, and undiagnosed abnormal genital bleeding.

Warnings—The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected the drug should be discontinued immediately.

Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis and pulmonary embolism and the use of oral contraceptives. There have been three principal studies in Britain[1-3] leading to this conclusion, and one[4] in this country. The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about sevenfold, while Sartwell and associates in the United States found relative risk of 4.4, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as nonusers. The American study also indicated that the risk did not persist after discontinuation of administration, and that it was not enhanced by long-continued administration. The American study was not designed to evaluate a difference between products. However, the study suggested that there might be an increased risk of thromboembolic disease in users of sequential products. This risk cannot be quantitated, and further studies to confirm this finding are desirable. Retrospective studies in Great Britain have shown a statistically significant association between cerebral thrombosis and embolism and the use of oral contraceptives. This has not been confirmed in the United States.



Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

Since the safety of Ovulen in pregnancy has not been demonstrated, it is recommended that for any patient who has missed two consecutive periods pregnancy should be ruled out before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule the possibility of pregnancy should be considered at the time of the first missed period.

A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time.

Precautions—The pretreatment and periodic physical examinations should include special reference to the breasts and pelvic organs, including a Papanicolaou smear since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals. Endocrine and possibly liver function tests may be affected by treatment with Ovulen. Therefore, if such tests are abnormal in a patient taking Ovulen, it is recommended that they be repeated after the drug has been withdrawn for 2 months. Under the influence of progestogen-estrogen preparations preexisting uterine fibromyomas may increase in size. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam adequate diagnostic measures are indicated. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. Any possible influence of prolonged Ovulen therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving Ovulen therapy. The age of the patient constitutes no absolute limiting factor, although treatment with Ovulen may mask the onset of the climacteric. The pathologist should be advised of Ovulen therapy when relevant specimens are submitted. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids.

Adverse reactions observed in patients receiving oral contraceptives—A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions: thrombophlebitis, pulmonary embolism and cerebral thrombosis.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, breast changes (tenderness, enlargement and secretion), change in weight (increase or decrease), changes in cervical erosion and cervical secretions, suppression of lactation when given immediately post partum, cholestatic jaundice, migraine, rash (allergic), rise in blood pressure in susceptible individuals and mental depression.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: anovulation post treatment, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption and itching.

The following laboratory results may be altered by the use of oral contraceptives: hepatic function: Increased sulfobromophthalein retention and other tests; coagulation tests: increase in prothrombin factors VII, VIII, IX and X; thyroid function: increase in PBI and butanol extractable protein bound iodine, and decrease in T^3 uptake values; metyrapone test and pregnanediol determination.

1. Royal College of General Practitioners: Oral Contraception and Thromboembolic Disease, J. Coll. Gen. Pract. *13*:267-279 (May) 1967.
2. Inman, W. H. W., and Vessey, M. P.: Investigation of Deaths from Pulmonary, Coronary, and Cerebral Thrombosis and Embolism in Women of Child-Bearing Age, Brit. Med. J. *2*:193-199 (April 27) 1968.
3. Vessey, M. P., and Doll, R.: Investigation of Relation Between Use of Oral Contraceptives and Thromboembolic Disease. A Further Report, Brit. Med. J. *2*:651-657 (June 14) 1969.
4. American Journal of Epidemiology (to be published).

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Editorials

Family Practice and Specialty Practice

PHYSICIANS AND OTHERS concerned with the community needs for more medical generalists sometime blame medical school specialists for the shortage. Such a simple explanation ignores at least one major associated cause: the increasing competence of the physician in practice. My thesis is that the improving diagnostic and therapeutic capabilities of practicing physicians are the most important factor promoting the trend away from general practice toward specialized practice of medicine. This thesis is based on fifteen years of observation at the University Medical School—as medical student, resident, and staff physician.

The practice of medicine observed by medical students in past years was largely care of indigent patients and a small number of private patients. Gradually, over the years, the number of indigent patients decreased and, as the skill of general and specialized physicians increased, fewer and fewer private patients were referred to the University Hospital. At the same time the patients referred were selected more and more from a smaller and smaller number of disease problems with which the physician in practice needed help.

Physicians on the University staff responded to the change in the pattern of disease problems in the patients referred and the need for more knowledge of how to handle these problems. The University physicians set up new specialty clinics and became sub- (or super-) specialists within conventional specialties.

The result is that medical students are being exposed to high concentrations of narrow disease problems at the time when they are forming their attitudes and interests in medical practice. They tend to be attracted to the fields of interest of the professors, whose special areas have developed from the problems of the physician in practice, as defined by the type of diseases referred to the University by the physician in practice.

Therefore, the physician in practice should not only point a finger at the University when the decreased number of generalists is mentioned; he should also ask himself: who was the last patient he referred to the University, what was that patient's disease problem, and whether the student who was training to care for that patient is likely to become the doctor next door.

Today the University physicians are becoming more concerned about their responsibilities toward the physicians in practice and the patients in the community. I believe there is an even greater need for the practicing physicians to become concerned about their responsibilities toward the physicians in the University Medical School and the medical students in training. Perhaps the new Family Practice Program at the University Medical School can become the medium for fresh conversation and new cooperation among the practicing physician, the University physician, the community and the College of Medical Sciences.

Warren J. Warwick, M.D.*
Minneapolis, Minnesota

*Associate Professor, Department of Pediatrics, University of Minnesota, Minneapolis, Minnesota.

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Diastolic Augmentation in Nature

Doctors Moulopoulos, Kwan-Gett, Collan and Kolff* report favorable results using intra-aortic balloon diastolic augmentation in sheep with ligated coronary arteries. Although currently challenged by technical problems, the idea works.

Intra-aortic balloon pumping during ventricular diastole augments the heart by displacing blood from the aorta. With proper timing aortic pressure is thereby lowered when the ventricle begins its next contraction. Then ventricular pressure quickly exceeds the lowered aortic pressure, opening the aortic valve earlier in systole. Energy otherwise spent on isometric contraction becomes available for dynamic contraction. In this manner stroke volume increases without additional cardiac energy. The same hemodynamics apply in normovolemic anemia where aortic pressure falls rapidly between ventricular contractions due to the low peripheral resistance. Thus the increased cardiac output of anemia can be considered "augmented" also.

Nature provides each species with an intricately balanced hemodynamic system. For instance, sheep have red blood cells only 4.8 microns in diameter, an average RBC count of million/cu mm, a hematocrit of 32%, a blood hemoglobin of 10.9 gm%[1] and an oxyhemoglobin dissociation curve favoring dissociation.[2] These characteristics result in a low blood viscosity and a low blood oxygen-carrying capacity relative to man. The low blood viscosity lowers vascular resistance and increases cardiac output. Since the volume of oxygen delivered to the issues is the product of blood flow and blood oxygen content, sheep are not at a great disadvantage. Also, the oxyhemoglobulin dissociation curve of sheep (approximated by that seen in chronically anemic humans) results in greater oxygen extraction. Certainly "diastolic augmentation" operates normally in sheep relative to man. Even so, hemodynamic changes in these studies should be significant. However, hematocrit variation during the experimental period is a crucial and neglected point.

Ernest Ruiz, M.D.
Minneapolis, Minnesota

*See page 261.

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1. Wintrobe, M. M. in Handbook of Respiration, edited by D. S. Dittmer and R. M. Grebe. Philadelphia, W. B. Saunders Co., p. 104, 1958.
2. Lambertson, C. J., Bunce, P. L., Drabkin, D. L. and Schmidt, C. F. Ibid. p. 80.

Laboratory Medicine

Laboratory medicine is now able to make contributions in diagnosis and management of patients, which are more extensive and crucial than ever before. Unfortunately much of this potential is not now realized, due in large measure to physicians' bewilderment over the increasing complexity of the laboratory armamentarium. Their failure to utilize strategically all of the support laboratory medicine can now offer them limits their diagnostic ability and capacity to manage patients with the utmost skill.

Laboratory physicians, chiefly clinical pathologists, are now closing this gap, however. By training and experience these individuals have a thorough knowledge of the clinical laboratory disciplines and also of medicine and the diagnostic requirements of patient care.

The rapidly increasing potential of laboratory medicine has resulted from outstanding technological advances, especially in the area of automation, and from crucial advances in sciences basic to medicine.

Technological advances in recent years have provided rapid and precise analyses. Batteries of tests are now available for screening purposes on patients entering the hospital and for those seen in doctors' offices. Specific screening batteries are now becoming available for discrete diagnostic purposes, such as the analysis of suspected liver disease.

Quality control methods now in general use in well operated clinical laboratories assure precision of results reported to the physician.

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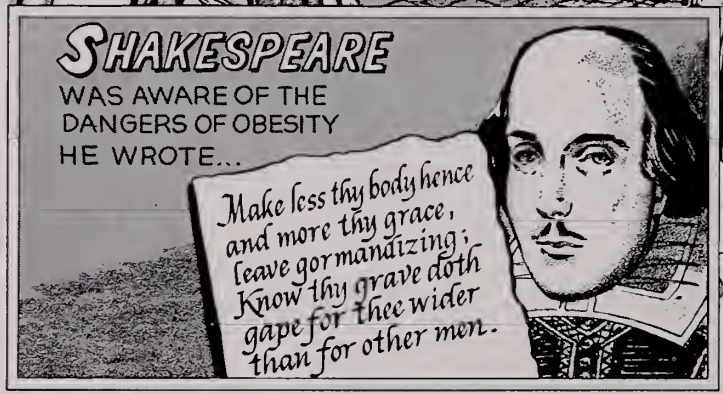
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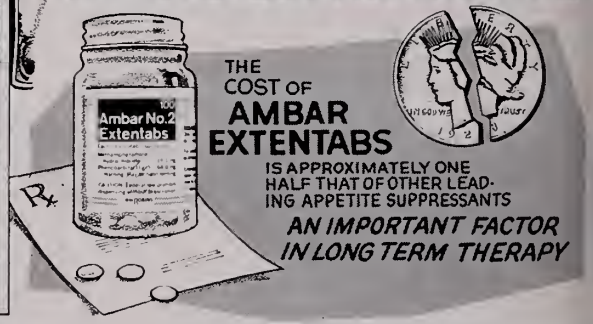


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Accordingly, attention is being directed toward normal values and ranges. The meaning of "normal" is being reassessed and refined, and standards of comparison will be improved with consequent increase in the potential usefulness of laboratory procedures.

In the generation and use of laboratory data, automatic data processing is becoming a fundamental reality. The use of computers provides not only more rapid and accurate reporting but also better display and use of data, especially in terms of statistical comparison with previous trials on an individual patient and comparison with the "normal state."

Many important advances crucially relevant to medicine have been made in basic sciences, especially in biochemistry, molecular biology and cell biology. Their application to medicine have resulted in important discoveries highly relevant to patient care: for example, the discovery of the hemoglobinopathies, of red cell metabolic defects, such as glucose-6-phosphate deficiency, underlying hemolytic disease, and of the role of 2, 3 glycerol diphosphate in hypoxia. Numerous advances in the treatment of disease states rely heavily on developing knowledge in basic science fields. The dependence of organ transplantation on increasing understanding of the antigen-antibody reaction is a notable example.

There are many more examples of the relevance of laboratory medicine to the daily practice of medicine: for example, improvements in technology that make it possible not only to detect pathogenic micro-organisms (in urine, for example) and to identify them but also to predict their antibiotic sensitivity much more rapidly than in the past.

In the light of the circumstances I have discussed, the series on Laboratory Medicine initiated in this issue of MINNESOTA MEDICINE,* is both timely and important. These articles, the first by Dr. Charles Horwitz and Melvin Sinykin, will be written by physicians for physicians and will bring to the readers' attention many notable practical advances in laboratory medicine and their contribution to patient care.

Ellis Benson, M.D.
Minneapolis, Minnesota

*See page 311.

Hypertension: Who? Why? What?

THREE ARTICLES appearing in the August issue of MINNESOTA MEDICINE suggest answers to the three questions posed above. The first article, by Wilber and Barrow,* relates the results of a random community study of high blood pressure. They found that about half the patients with hypertension were completely unaware of it. More appalling, approximately half of those who knew they had hypertension were not on treatment owing to failure to continue medication. The authors attempted to remedy this by an educational program, but even then approximately half the group stopped taking medicine. Thus it would appear that an important segment of the population is not receiving adequate treatment for hypertension and that much of the fault lies in the patient himself.

The second article, by Armstrong and colleagues,† reports the results of a double blind study of drug treatment in a large group of veterans who had significant increase of blood pressure but no exudates or papilledema in the optic fundus. This study leaves no doubt whether such patients benefit from therapy: In 73 drug-treated patients only two adverse events as defined by the authors occurred, while in 70 placebo-treated patients 27 such adverse events occurred. The effect of treatment was so evident to the investigators that

*Wilber J. A., and Barrow, J. G.: Reducing Elevated Blood Pressure. Minnesota Med. 52:1303, 1969.

†Armstrong, M. L., Tewksbury, R. B., Shaw, L. W., and Freis, E. D.: Veterans Administration Multiclinic Trial of Drug Treatment in Hypertension. Minnesota Med 52:1297, 1969.

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References: 1. Jaffe, J. H.: in Goodman, L. S., and Gilman, A.: The Pharmacological Basis of Therapeutics, 3rd ed., 1965, pp. 279-280. 2. Woods, L. A., in Drill, V. A.: Pharmacology in Medicine, 1958, pp. 226-227. 3. Goth, A.: Medical Pharmacology, 2nd ed., 1964, pp. 336-337. 4. Beckman, H.: Pharmacology, 2nd ed., 1961, pp. 180-183. 5. LaBrecque, D. C.: Curr. Ther. Res. *8*: 106-109, 1966. 6. Dunlop, E.: J. Amer. Geriat. Soc. *16*:343-349,1968.

they stopped the study before completion because the untreated patients were having so much difficulty.

The third article, by Tobian,* outlines a practical approach to the medical therapy of hypertension. Such therapy has become quite stereotyped in that most patients are started on a thiazide; then either alpha-methyldopa or reserpine is added to the program, and finally, in severe hypertension, guanethidine also is added.

With potent drugs now available, a primary problem in the treatment of hypertension is lack of patient cooperation. A patient needs to undergo a series of tests to determine whether he has sustained hypertension and, if so, whether it is of a secondary variety. He should understand why he needs the treatment for a disease that he himself cannot recognize and that does not affect his feeling of well-being. He has to learn to tolerate taking pills every day and the side effects these pills may cause. He must do all of this because of something that might happen to him in the future.

It appears then that one of the primary problems today is patient education. The national community has become more medically sophisticated regarding the evils of cancer, smoking, high cholesterol, and obesity, but it has not learned much about the dangers of hypertension. It is evidently necessary for the doctor treating high blood pressure to spend as much time in educating the patient as in any other facet of the therapy.

Mahlon K. Burbank, M.D.
Rochester, Minnesota

*Tobian, Louis: Modifying Elevated Blood Pressure. Minnesota Med. 52:1307, 1969.

Test Your Word Score

Dysplasia—*abnormal tissue development* (page 245).

Orthotic—*straightening* (page 248).

Calyces—*infundibula—pelves of the kidney* (page 254).

Agnogenic—*idiopathic* (page 257).

De novo—*from the beginning* (page 257).

Solenoid—*a coil of wire spaced equally between turns, acting as a magnet when current flows through* (page 262).

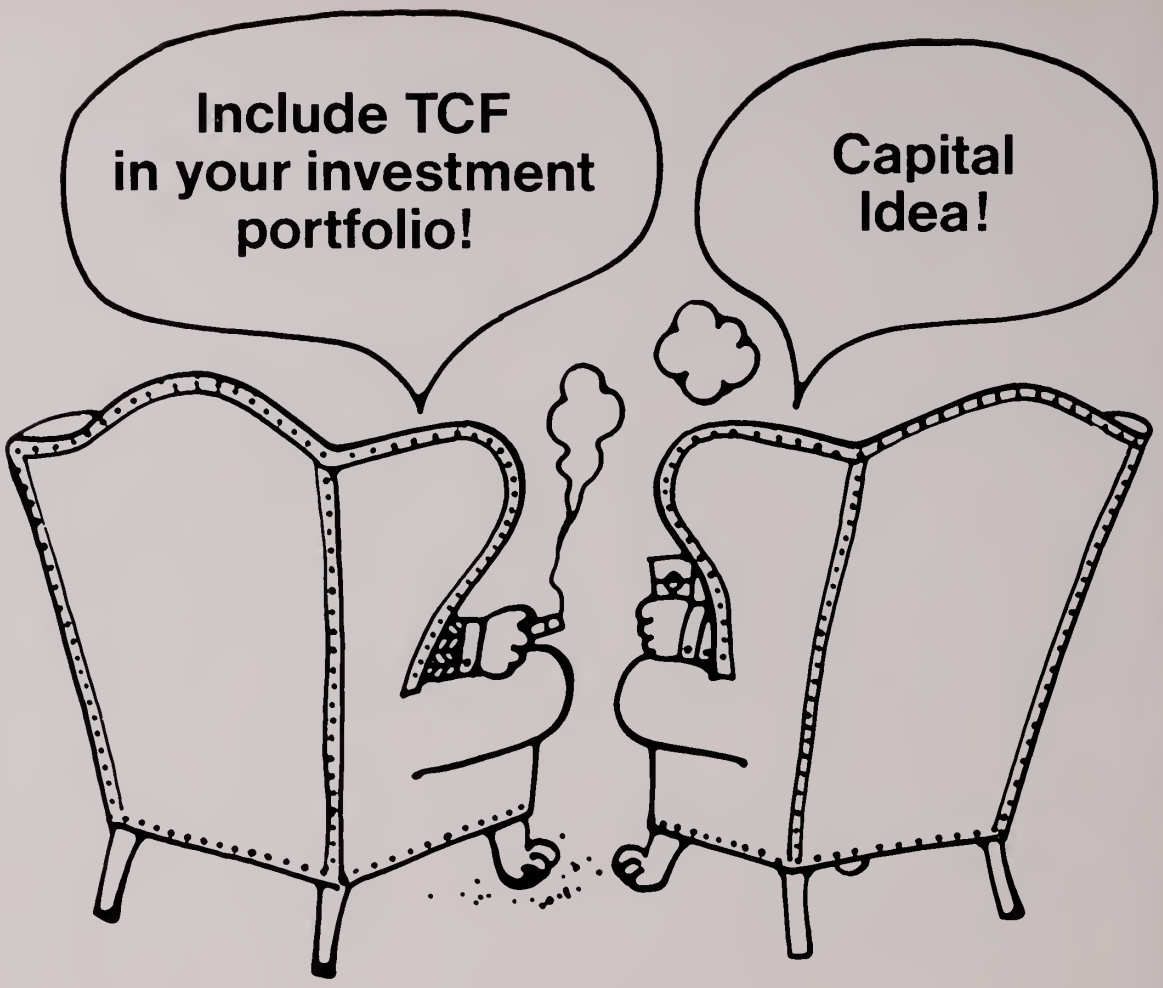
Appurtenance—*something subordinate to another more important thing* (page 266).

Torque—*a rotary force* (page 295).

Somnolence—*sleepiness* (page 315).

Vivax malaria—*due to Plasmodium vivax, producing tertian malaria* (page 331).

Falciparum malaria—*due to Plasmodium falciparum, producing estivo-autumnal fever* (page 331).



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The Editor's Soliloquy

Tilting at Windmills?

Our State Medical Association dues are only $100. Michigan's are $175; Wisconsin's, $145; South Dakota's, $125; North Dakota's, $125; Iowa's, $150. Great Northern Railway employees pay $65.00 in annual dues; Twin City Rapid Transit Company employees, $72; Minneapolis Gas Company employees, $48. Barbers are assessed $76 a year for the prerogative of union membership; and construction workers are gratified to have and to hold their jobs—at up to $120 a year for the privilege of being members in their union.

Perhaps you have never thought to ask what perquisites are included in your $100 dues. Well, neither had I until my wife goaded me into wondering. She pays the bills; I just make the living. I tell her I'm too busy—practicing, studying, reading, reviewing medical books, trying to uphold and further enhance the image of us doctors.

Well, here are some of the facts. There are 23 fulltime employees in our State office. They all work for you like busy beavers and that costs a pretty penny: not an incommensurate stipend, however, for their substantial operation.

There are 21 scientific and 26 nonscientific committees composed of your peers, involving the services of 846 doctors who meet two or more times a year, working one or two long eight-hour days to solve some of the complex problems that make your practice a breeze. These doctors receive neither remuneration for their services nor reimbursement for expenses incurred, though they are provided with coffee and snacks throughout the day and a complimentary heart-warming dinner at the close of their fully occupied day.

Now I know that you can't file the result of these numerous committee activities in your office files, and you can't deposit them in the bank. You can't schedule a bridge party, a golf game, a hunting expedition, or a Caribbean cruise with any of these relatively silent partners whom you so grudgingly support; but only because of them is it possible for you to engage in those very recreations with friends of your own choosing.

These conscientious, hard-working committee members thrive on their responsibilities. They are the organization men: the planners, the doers, the team-work operators. They move up in the chairs; they have friends and influential contacts available, and they use them to your advantage.

What would you do if you had to spend 80 man-hours to save yourself $175 on an insurance premium, How would you manage 78 man-hours appraising the problems of public sanitation in your own community?

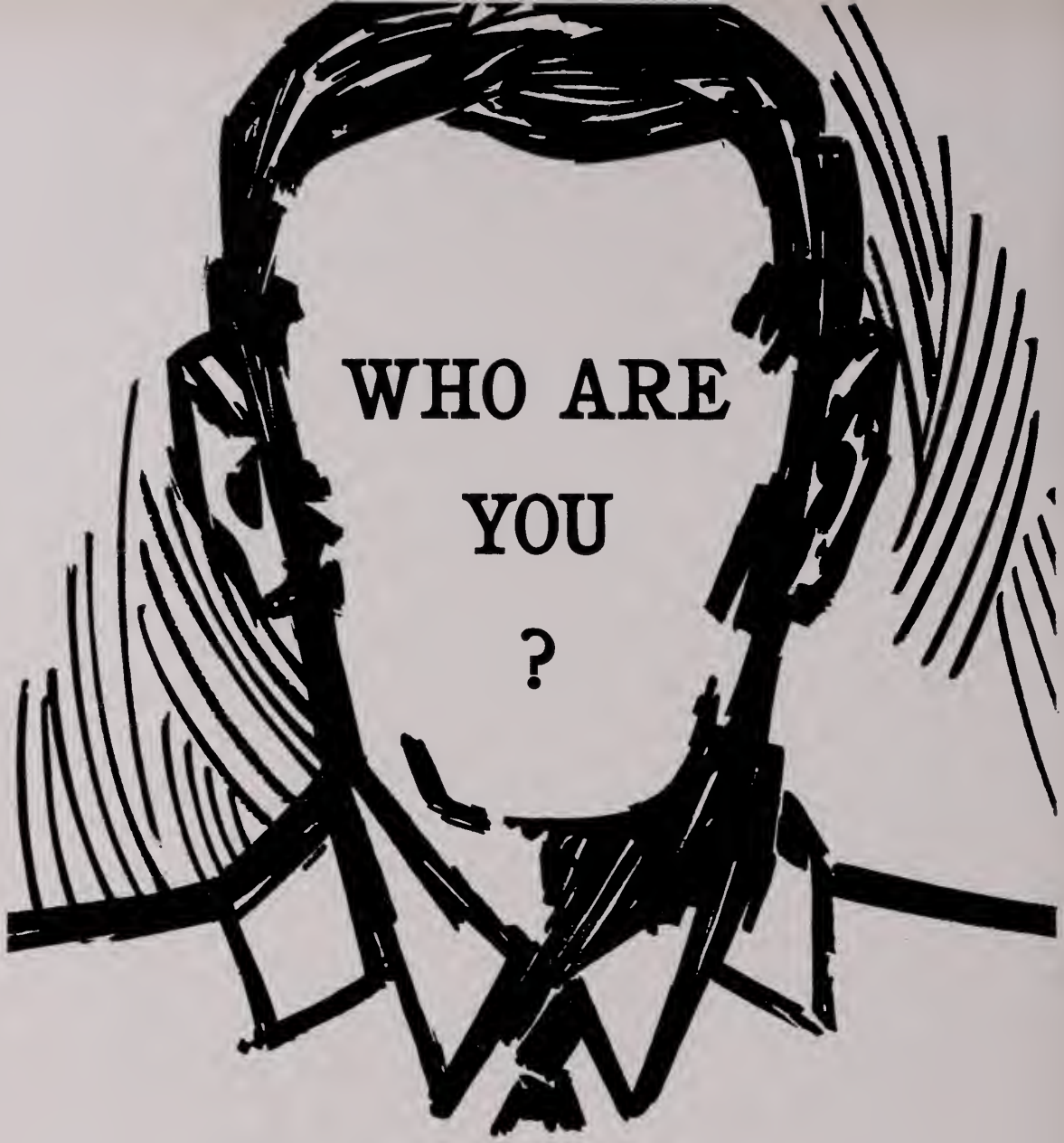
With all of these problems confronting and challenging you right on your own doorstep I wager you'd prefer to return to the stringencies of house calls, after-office hours, and all-night telephone interruptions.

As for me, I prefer to practice private medicine instead of assuming committee responsibility. I enjoy my hospital rounds, clinical work, office patients, books, medical journals, and my editorship of Minnesota Medicine.

Incidentally, why should our dues be less than South Dakota's? Aren't we as willing or as affluent? I make a motion we raise them.* **Carl O. Rice, M.D.**

*See page 336.

OLD DOC HESS SAYS: If you interject anger into your opinion you lose much of its value.—C.O.R.



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Curbstone Consultation

Adenocarcinoma of the Rectum

QUESTION: I have a 62-year-old male patient with adenocarcinoma of the rectum located at 6 centimeters from the anal verge. He steadfastly refuses abdominoperineal resection. Is there any evidence that electrocoagulation of the tumor (4 x 4 cm. in size) would provide palliative relief? If so, should this procedure be carried out at this time for prophylactic relief or be deferred until such time as the patient develops bleeding or other symptoms?

ANSWER: Electrocoagulation for the treatment of rectal carcinoma has been proposed as a definitive procedure for many years. Recent proponents for this mode of therapy include Madden and Kandalaft.* They treated 28 patients of whom 17 (60.7%) were alive and well one to 13 years (average of 49.6 months) following treatment. It has been proposed that the necrotic tumor tissue produced by electrocoagulation may assume antigenic properties which stimulate a specific antibody response, and certain experimental work and clinical evidence supports this view†. Thus, it is reasoned that even though lymph nodes were involved by metastatic cancer cells, the autovaccine produced by fulguration would inhibit their growth or destroy them. It would seem advisable to apply this form of treatment early rather than wait for the development of symptoms in the case in question.

Harold D. Kletschka, M.D.
Montgomery, Alabama

*Ann Surg 166:413, 1967.
†Strauss et al. Surg Gynec Obstet 121:989, 1965.

Petty Annoyances

It's the little things that bother
And put us on the rack:
You can sit upon a mountain,
*But not upon a tack.**

*Maxwell Droke: The Speaker's Handbook of Humor.

Some people are so sensitive that they feel snubbed if an epidemic overlooks them.—Frank McKinney Hubbard.



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The Viewing Box

Constipation

THIS 60-YEAR-OLD white female complained of constipation and some tarry stools. Proctoscopy showed a polypoid tumor at 16 cm. which was interpreted clinically as carcinoma. The patient was admitted for resection.

What is your diagnosis? (See next page.)



Figure 1

Diagnosis: Pneumatosis Cystoides Intestinalis.

This 60-year-old lady initially had complaints of constipation and some melena. She had had proven chronic duodenal ulcer and intermittent gastrointestinal bleeding before the current visit. Colon studies done prior to anticipated resection show small pneumocysts in the rectosigmoid area (Figure 1, arrows). Biopsy of the "rectal mass" substantiated the diagnosis and the patient was discharged on conservative therapy for duodenal ulcer. She was readmitted two years later with a history of increasing obstipation and intermittent episodes of obstructive symptomatology. Barium enema at this time showed the marked progression of the pneumatosis intestinalis involving the sigmoid and rectosigmoid portions of the distal (Figure 2) colon. The patient is not improving with conservative therapy and resection is anticipated.

Pneumatosis intestinalis is a relatively uncommon condition, characterized by the presence of multiple gas-filled cysts in a portion of the gastrointestinal tract and occasionally in other organs of the abdominal cavity. This entity occurs at all ages and in both sexes, but is seen most commonly between the ages of 30 and 50 in males, in the sixth decade in females, and in infants be-



Figure 2

tween the ages of two weeks and 14 months. Cysts are located either subserously or, less commonly, submucosally. The proximal small bowel is the most common site of involvement, followed by the ileocecal area and the colon in that order of frequency. This has also been seen in the stomach, duodenum, omentum, peritoneum, liver and gallbladder, mesenteric lymph nodes, beneath the parietal peritoneum of the kidneys, peritoneum of the lesser pelvis, and even in vaginal walls and in the inguinal canals.

Elliot and Elliot[1] have shown by experimentation that the visceral compartment of the deep cervical fascia is closed and that the only possible decompression of a silent tension pneumomediastinum from a painless alveolar rupture is via the sheaths of the pulmonary arteries which connect with the fascial sheath of the aorta. The suction and pulsion in the thorax propel the air down the fascial sheaths of the aorta in the segmental distribution of its main branches throughout the abdomen which then account for a list of radiographic signs which are described in the article, including: paravertebral air in the mediastinum; an air strip outlining the stomach in a double ring contour; multiple grape-like bubbles of translucency mixed with small bowel gas shadows; serosal and submucosal bullae within the colon; air in the lateral abdominal walls, along the inguinal canals and tracking along the iliofemoral arterial fascial sheaths; as well as silent pneumoperitoneum typically without peritonitis which is extremely characteristic of this entity. Review of this article is strongly recommended.

The pneumocysts become lined by a syncytium of tissue phagocytes which form the pseudolymphatic spaces. The phagocytic nature of these cells has been substantiated by special staining techniques.

Pneumotosis is usually a recurrent process and is generally asymptomatic. Several authors feel it is much more common than now appreciated. If we look for the signs suggested by Elliot and Elliot it is likely this entity will be diagnosed more frequently.

Donald R. Mueller, M.D.*
Grand Rapids, Minnesota

*Department of Radiology, Itasca Memorial Hospital.

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1. Elliot, G. B., and Elliot, K. A.: Pneumatosis Cystoides Intestinalis. Amer J Roentgenol Rad Therapy & Nuclear Med 89:87, 728.
2. Bockus, Henry L.: Gastroenterology.

Ethics

About the best method of climbing higher is to remain on the level.
—Advertiser's Digest.

Man

Man is a little soul carrying around a corpse.—Epictetus

Without labor nothing prospers.—Sophocles

Nothing can hold liquor as well as a bottle. So leave it in the bottle.—Rail and Tie

Medical Terms and Their Lay Synonyms

(Continued from January issue*)

Bowel sewage—*feces*

Box of ivories—*good teeth*

Boxer's fracture—*fracture of the fifth metacarpal*

Bracelets—*transverse volar creases*

Bracers—*legs*

Brain fever—*encephalitis*

Brain shell—*skull*

Brain softening—*paresis*

Brand—*anus*

Brand mark—*vaccination scar*

Brandy face—*acne rosacea*

Branks—*parotitis*

Brawny arm—*lymphedema*

Bread basket—*stomach*

Break bone fever—*dengue*

Break wind—*eructation*

Breast complaint—*pulmonary tuberculosis*

Breathers—*lungs*

Brick layer's itch—*eczema*

Brick maker's anemia—*anclyostomiasis*

Bright's disease—*nephritis*

Brill's disease—*typhus fever*

Bring it away—*induce an abortion*

Brody—*a convulsion*

Broken breasts—*mastitis*

Broken windedness—*asthma*

Bronchial dilatation—*bronchiectasis*

Bronchocele—*goitre*

Bronze disease—*Addison's disease*

Brow ague—*migraine headache*

Brown kettles—*bronchitis*

Brown patches—*tinea versicolor*

Brucehart fever—*dengue*

Bruce's septicemia—*brucella infection*

Bubonic plague—*Pasteurella pestis infection*

Bucket fever—*dengue*

Buena—*yaws*

Bug farm—*tuberculosis sanatorium*

Bulbultis—*stammering*

Bull teaser—*rhinophyma*

Bull's eye—*umbilicus*

Bum lamps—*myopic eyes*

Bunion artist—*chiropodist*

Burfin—*delivery*

Burn bad powder—*expel flatus*

Burnt bulb—*amauretic eye*

Burnt lamps—*blind*

Bury a Quaker—*defecate*

Business—*defecating*

Butcher shop—*hospital*

Butcher's wart—*verruca necrogenica*

Eugene Benet, M.D.†
Syracuse, New York

*See page 100.
†Assistant Professor of Radiology, University of Syracuse Medical Center.



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References: 1. Gardner, H. L.: J. Miss. M.A. 8:529, 1967. 2. Porter, P. S., and Lyle, J. S.: Arch. Dermat. 93:402, 1966. 3. Walsh, H.; Hildebrandt, R. J., and Prystawsky, H.: Am. J. Obst. & Gynec. 93:904, 1965. 4. Vaginitis and the Pill: J.A.M.A. 196:731, 1966. 5. Guerriera, W. F.: South. M.J. 56:390, 1963. 6. Seelig, M. S.: Am. J. Med. 40:887, 1966. 7. Today's Drugs, New York, Grune & Stratton, Inc., 1965, p. 316. 8. Gray, L. A., and Barnes, M. L.: Am. J. Obst. & Gynec. 92:125, 1965. 9. Salerno, L. J.; Ortiz, G., and Turkel, V.: Vaginitis: A Diagnostic and Therapeutic Approach, Scientific Exhibit, presented at the 115th Annual A.M.A. Convention, Chicago, Illinois, June 1966. 10. Walsh, J. C.; Sheffery, J. B., and Wilson, T. A.: Med. Ann. D.C. 37:358, 1968. 11. Nugent, F. B., and Myers, J. E.: Pennsylvania Med. 69:44, 1966.

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Fracture Conference

Fractures of the Metacarpals

Case 1

Dr. Edwin L. Laurnen:

Our first patient is a 34-year-old housewife who forcibly bumped her left hand on a table two weeks before this x-ray was taken (Figure 1). She had pain over the ulnar aspect of the wrist.

Dr. Darrell E. Fisher:

The x-ray shows a fine line across the base of the fifth metacarpal that appears to be a fracture, possibly extending into the joint.

Dr. Ronald L. Linscheid:

Do you think that this is a very important articular fracture? How much motion normally occurs at the fifth metacarpal-hamate bone?

Fracture conference held June 10, 1968.



Fig. 1—Left hand of 34-year-old housewife who struck ulnar side of wrist on a table.

Dr. Fisher:

Most of the motion occurs in the opposition maneuver when the palm is forming a cup; 15 or 25° of motion is possible.

Dr. Linscheid:

Do you think the fracture would interfere with the motion in the joint?

Dr. Fisher:

I think it unlikely. The fracture is somewhat analogous to a fracture at the base of the fifth metatarsal, distal to the insertion of the peroneus brevis in the foot. The flexor carpi ulnaris and extensor carpi ulnaris both insert at the base of the fifth metacarpal. Forced radial deviation of the hand against the resistance of these muscles or a sharp blow on the ulnar aspect of the hand is the most probable mechanism of injury.

Dr. Richard T. Chiroff:

The lack of displacement would suggest that injury to the ulnar nerve would be unlikely. I think the fracture should be immobilized with a cast for three weeks.

Case 2

Dr. Laurnen:

The next patient is a 70-year-old woman who in August 1964 fell from a lawn chair, landing on her right hand (Figure 2-A).

Dr. Rogers C. Southall:

There is a fracture through the base of the fifth metacarpal, with slight

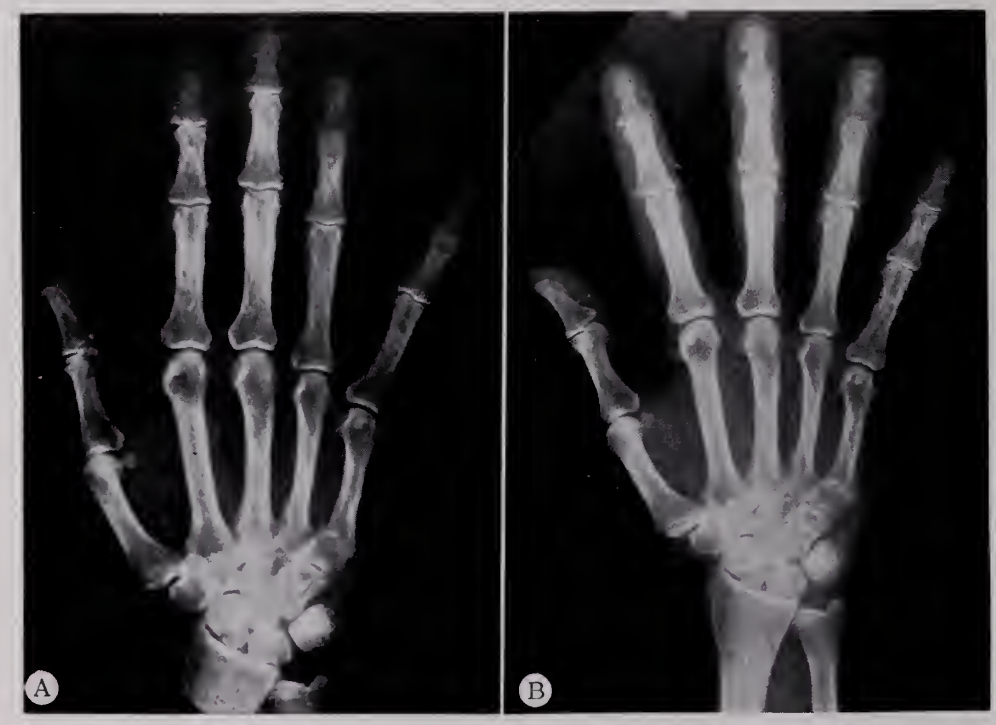


Fig. 2—(A) Right hand of 70-year-old woman who fell on right hand. (B) Four weeks after fracture of base of fifth metacarpal bone treated by cast immobilization.

displacement, and probably a fracture line at the base of the fourth metacarpal.

Dr. Linscheid:

How would you treat this painful fracture?

Dr. Southall:

I think that immobilizing it in a cast would be proper.

Dr. Laurnen:

A small amount of lidocaine was injected into the fracture site; the fracture was then reduced and a gauntlet cast applied.

Dr. Linscheid:

This elderly woman had extremely thin skin, and, even though we used a relatively well-padded cast, the parchment-like skin created a problem. There was also a tendency for her fingers to become stiff, even though we attempted to leave them free of the cast from the distal palmar line. The fracture healed satisfactorily without further difficulty in three weeks (Figure 2-B). As you can see, we do not have anatomic reduction, but there will be no disability.

Dr. Mark B. Coventry:

If this were a young man in his 30s, would you still be satisfied, or would you make further correction?

Dr. Linscheid:

I think I would still be satisfied. There is adequate motion at the fifth carpometacarpal joint to compensate for some malalignment. This would not bother the average person.



Fig. 3—(A) Right hand of 15-year-old girl who sustained sharp blow to ulnar aspect of hand. (B) Three weeks after fracture of shaft of fifth metacarpal bone.

Dr. Richard S. Bryan:

This type of fracture is like one at the base of the first metacarpal which occurs above the joint. Again you can allow a good deal of latitude in the reduction.

Case 3

Dr. Laurnen:

Our next patient is a 15-year-old girl who injured her right hand in July 1967. Her hand had been struck by a blow (Figure 3-A).

Dr. Allen P. Schlein:

There is a transverse fracture of the midshaft of the fifth metacarpal, with dorsal angulation at the fracture. You probably could hold reduction adequately with a snug cast.

Dr. Linscheid:

Is that the normal angulation for a fracture like that?

Dr. Schlein:

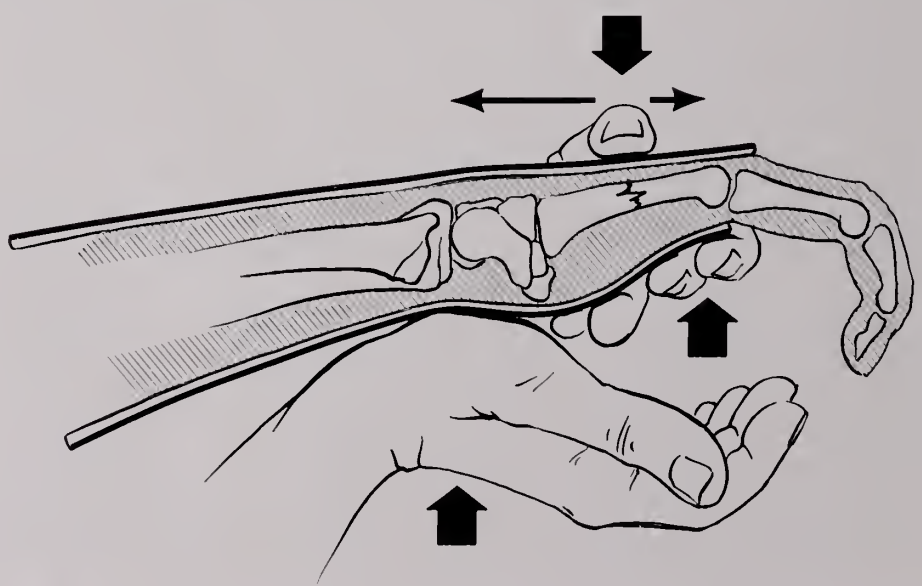
Yes. Most of the bulk of the intrinsic muscles is located volar to the axis of the metacarpal. When the metacarpal is fractured and the muscle is contused, the muscle undergoes some spasm, with a definite tendency to produce dorsal bowing. The extrinsic tendons also affect this result, as the long extensor is closer to the longitudinal axis of the bone than are the flexors. This combination of a larger movement of the arm and greater strength of the flexors thus induces a dorsal bowing. It would take a considerable force to volarly displace the fracture and leave it in that position.

Dr. Linscheid:

What is the probable mechanism of injury, Dr. Hirz? Could this be a fall on the outstretched hand?

Dr. Dale L. Hirz:

It is probably a fracture from a direct, laterally applied force, because an axial-loading type of fracture with stress longitudinally applied produces an oblique or spiral fracture. This fracture should be placed in a well-molded cast



C

Fig. 3—(C) Diagram showing fracture of the fifth metacarpal.

to apply three-point fixation to the angulated fracture, two volar areas (distal and proximal to the fracture), and one dorsal area directly over the fracture. Securing a snug cast is aided by molding with the heel of the hand dorsally while using the fingers of the same hand to mold a concave surface in the palm and at the same time flattening the volar surface of the plaster at the wrist with the other hand (Figure 3-C).

Dr. Laurnen:

The next x-ray shows the fracture at three weeks, and it appears to be healing (Figure 3-B). There is still some dorsal angulation despite the fracture being reduced and molded strongly.

Case 4

Dr. Laurnen:

The next patient is an eight-year-old boy who in September 1967 sustained a dog bite to the right hand and presented to the emergency room with open wounds on the dorsal and volar aspects of his hand (Figure 4-A).

Dr. Linscheid:

Dr. Paarlberg, would you describe this fracture and tell us what you would do, bearing in mind that there is an open wound?

Dr. Donald Paarlberg:

Obviously because it is a dog bite, you should debride the wound and wash it very carefully. In a child, the periosteum will generally hold a fracture once the bone slips back into place. So after debriding the wound, it would be wise to reduce the fracture and see how stable it is.

Dr. Linscheid:

This is what was done (Figure 4-B). Without fixation internally, the

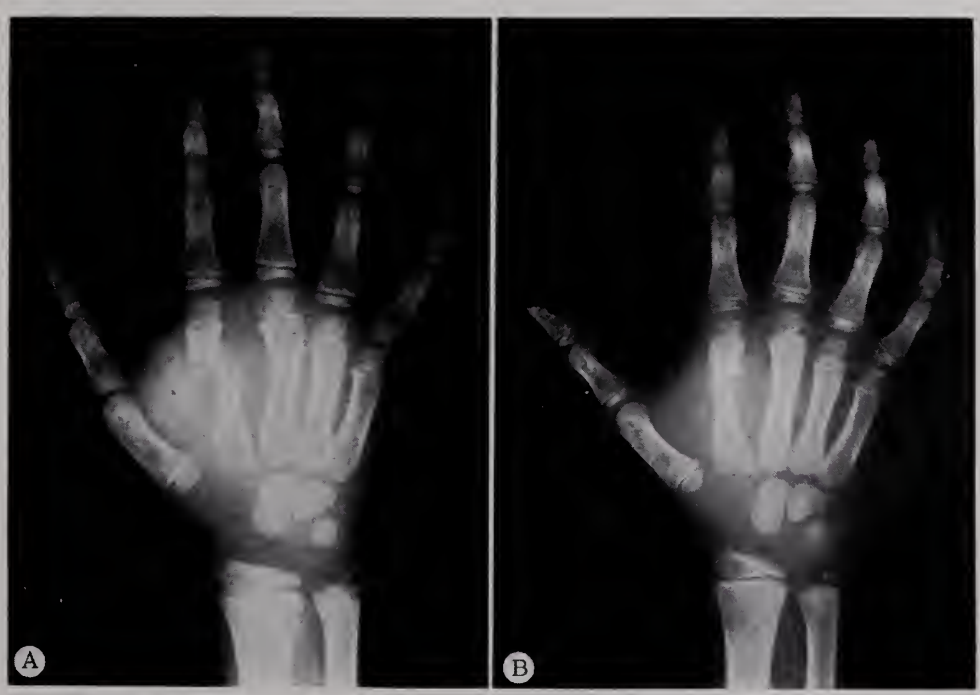


Fig. 4—(A) Dog-bite injury to shaft of second and third metacarpal bones in an eight-year-old boy. (B) Four weeks after debridement and cast immobilization.

fracture was aligned rather well, as you can see in the anteroposterior view. In an oblique view, the fracture was slightly angulated.

Dr. Paarlberg:

Normal growth would take care of that, but you would want to be sure that the position is correct as far as rotation is concerned. This can be done by flexing the patient's fingertip down and being sure that the fingertip points to the scaphoid tuberosity.

Dr. Linscheid:

The best place to achieve adequate reduction is in the emergency room where there is an x-ray technician. You can help position the patient's hand, and the film can be processed rapidly to give you the requisite information.

Case 5

Dr. Laurnen:

The next patient is a 29-year-old man who in June 1968 while playing softball slammed his left hand against the ground (Figure 5-A).

Dr. James A. Turner:

The mechanism of this injury could be an axial stress applied to the metacarpal heads. He could have fallen, striking the dorsum of the hand, but such a fall would not explain the rotation.

Dr. Linscheid:

Would you anticipate the metacarpophalangeal joints to be extended or flexed from an injury like that?

Dr. Turner:

They would be flexed, because, with the metacarpophalangeal joint down, the collateral ligaments are the tightest. If you then twist the hand with the



Fig. 5—(A) Injury sustained by 29-year-old man who jammed his left hand against the ground while playing softball. (B) After reduction and cast application.

proximal phalanges trapped against the ground, you can deliver a lot of torque* to the metacarpals. So these are probably torque fractures, with the metacarpophalangeal joints flexed.

I would expect this fracture to be relatively stable. You could treat it by inserting longitudinal K-wires, but this would not do much for the length relationship. Another alternative would be to use transverse K-wires, pinning the distal fragments to the adjacent metacarpals. Or you could treat the fracture conservatively by casting.

Dr. Linscheid:

When Cotton wrote one of the first articles in this country concerning hand fractures, he stated that metacarpal fractures rarely need any treatment, because no matter what position the metacarpals are in, they heal, and the function of the hand will be satisfactory. But I think this is a statement to which we would take exception today.

Dr. Turner:

The amount of shortening should not be much of a problem. There is not much intrinsic imbalance, primarily because the dorsal interossei are about equally shortened on both sides. As they are primarily phalangeal-inserting tendons, there is little effect on the intrinsic mechanism. The same amount of shortening in the proximal phalanx might give considerable intrinsic imbalance. If you treat this patient conservatively, you might put traction on the metacarpals via the phalanges, with resulting skin traction.

Dr. Linscheid:

Would you pull the finger just straight out, as with a banjo splint?

Dr. Turner:

That leads to a few complications, particularly stiff digits. The other method would be to use some type of skeletal traction. It is difficult to apply traction directly to the metacarpal, but it can be applied indirectly by flexing the finger around a splint that is anchored to a snug cast. You cannot apply traction very effectively around the corner, however.

Dr. Linscheid:

This man was treated by flexing the fingers over Alumina-foam splints incorporated into a snug gauntlet cast. A slight loss of length occurred (Figure 5-B). Fixation with Kirschner wiring after adequate reduction certainly would be acceptable. I am not very keen on the use of either skeletal, pulp, or nail traction in this type of fracture. Maybe you have some other ideas, Dr. Bryan.

Dr. Bryan:

I still use traction if I am working on the long finger, particularly the right. But I would not use it on the other fingers because it is not usually necessary. I certainly think that the little finger is hard to pull around the corners, but skeletal, not pulp, traction should be used. Pulp traction causes more troubles than other types of traction.

Ronald L. Linscheid, M.D.†
Edwin L. Laurnen, M.D.†
Einer W. Johnson, Jr., M.D.†
Rochester, Minnesota

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*See Test Your Word Score, Page 277.

†Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

The Humanities

Health Regime

"There is a wisdom in this beyond the rules of physic: a man's own observation, what he finds good of, and what he finds hurt of, is the best physic to preserve health.

Act Your Age

But it is a safer conclusion to say, 'This agreeth not well with me, therefore I will not continue it;' than this, 'I find no offence of this, therefore I may use it.' For strength of nature in youth passeth over many excesses, which are owing a man till his age. Discern of the coming on of years, and think not to do the same things still; for age will not be defied.

Moderation

Beware of sudden change in any great point of diet, and if necessity inforce it, fit the rest to it. Examine thy customs of diet, sleep, exercise, apparel, and the like; and try, in any thing thou shalt judge hurtful, to discontinue it by little and little. To be free-minded and cheerfully disposed at hours of meat and of sleep and of exercise, is one of the best precepts of long lasting.

Clean Mind

As for the passions and studies of the mind; avoid envy; anxious fears; anger fretting inwards; subtle and knotty inquisitions; joys and exhilarations in excess; sadness not communicated. Entertain hopes; mirth rather than joy; variety of delights, rather than surfeit of them; wonder and admiration, and therefore novelties; studies that fill the mind with splendid and illustrious objects, as histories, fables, and contemplations of nature.

Dissipation

If you fly physic in health altogether, it will be too strange for your body when you shall need it.

Illness

Despise no new accident in your body, but ask opinion of it. In sickness, respect health principally; and in health, action. For those that put their bodies to endure in health, may in most sicknesses, which are not very sharp, be cured only with diet and tendering.[1]

Longevity

Celsus could never have spoken it as a physician, had he not been a wise man withal: use fasting and full eating, but rather full eating; watching and sleep, but rather sleep; sitting and exercise, but rather exercise; and the like.

A Wise Physician

Physicians are some of them so pleasing and conformable to the humor of the patient, as they press not the true cure of the disease; and some other are so regular in proceeding according to art of the disease, as they respect not sufficiently the condition of the patient. Take one of a middle temper; or if it may not be found in one man, combine two of either sort; and forget not to call as well the best acquainted with your body, as the best reputed of for his faculty.[2]"

[1]Nursing
[2]Ability

Essays of Francis Bacon, Harvard Classics.



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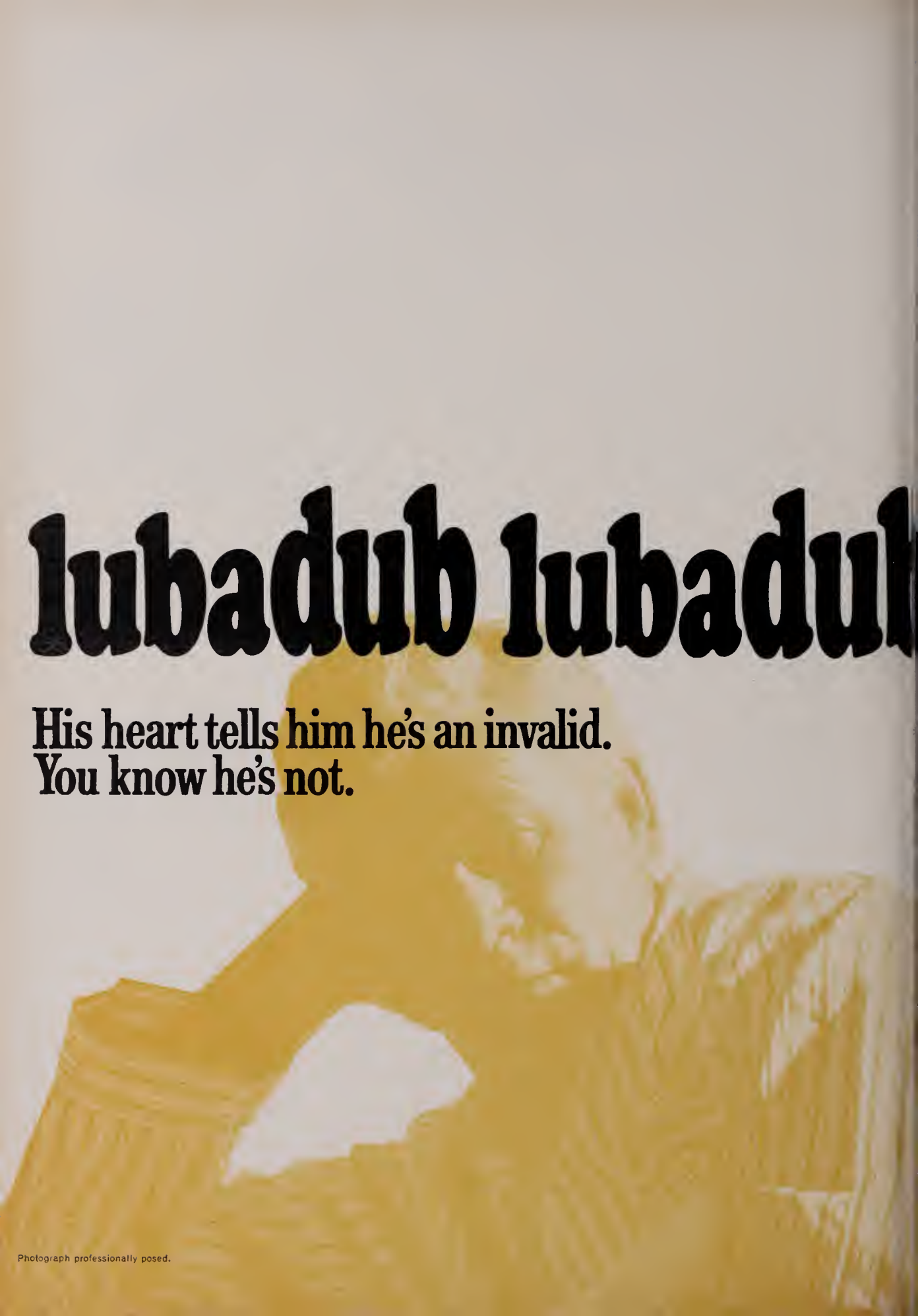
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Important Precautions: Carefully supervise dose and amounts prescribed, especially for patients prone to overdose themselves. Excessive prolonged use has been reported to result in dependence or habituation in susceptible persons, as alcoholics, ex-addicts, and other severe psychoneurotics. After prolonged excessive dosage, reduce dosage gradually to avoid possibly severe withdrawal reactions. Abrupt discontinuance of excessive doses has sometimes resulted in epileptiform seizures.

Warn patients of possible reduced alcohol tolerance, with resultant slowing of reaction time and impairment of judgment and coordination.

Reduce dose if drowsiness, ataxia or visual disturbance occurs; if persistent, patients should not operate vehicles or dangerous machinery.

Side Effects include drowsiness, usually transient; if persistent and associated with ataxia, usually responds to dose reduction; occasionally concomitant CNS stimulants (amphetamine, mephentermine sulfate) are desirable. Allergic or idiosyncratic reactions are rare, but such reactions, sometimes severe, can develop in patients receiving only 1 to 4 doses who have had no previous contact with meprobamate. Previous history of allergy may or may not be related to incidence of reactions. Mild reactions are characterized by itchy urticarial or erythematous maculopapular rash, generalized or confined to groin. Acute nonthrombocytopenic purpura with cutaneous petechiae, ecchymoses, peripheral edema and fever have been reported. One fatal case of bullous dermatitis following intermittent use of meprobamate with prednisolone has been reported. If allergic reaction occurs, meprobamate should be stopped and not reinstituted. Severe reactions, observed very rarely, include angioneurotic edema, bronchial spasms, fever, fainting spells, hypotensive crises (1 fatal case), anaphylaxis,

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iety is expected in the cardiovascular patient.
tle may even be desirable.

when anxiety is exaggerated . . . when it
feres with sleep . . . when it aggravates
liovascular symptoms, your help may
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urally, you'll want to reassure the patient.

perhaps prescribe Equanil (meprobamate)
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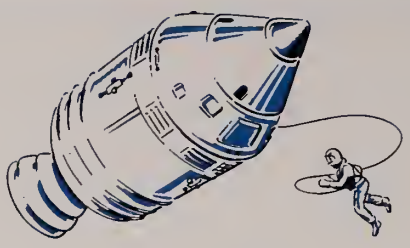
stomatitis and proctitis (1 case) and hyperthermia. Treat symptomatically as with epinephrine, antihistamine and possibly hydrocortisone. Aplastic anemia (1 fatal case), thrombocytopenic purpura, agranulocytosis and hemolytic anemia have occurred rarely, almost always in presence of known toxic agents. A few cases of leukopenia, usually transient, have been reported on continuous administration.

Meprobamate may sometimes precipitate grand mal attacks in patients susceptible to both grand and petit mal. Extremely large doses can produce rhythmic fast activity in the cortical pattern. Impairment of accommodation and visual acuity has been reported rarely. After excessive dosage for weeks or months, withdraw gradually (1 or 2 weeks) to avoid recurrence of pretreatment symptoms (insomnia, severe anxiety, anorexia). Abrupt discontinuance of excessive doses has sometimes resulted in vomiting, ataxia, tremors, muscle twitching and epileptiform seizures. Prescribe very cautiously and in small amounts for patients with suicidal tendencies. Suicidal attempts have resulted in coma, shock, vasomotor and respiratory collapse and anuria. Excessive doses have resulted in prompt sleep; reduction of blood pressure, pulse and respiratory rates to basal levels; and occasionally hyperventilation. Treat with immediate gastric lavage and appropriate symptomatic therapy. (CNS stimulants and pressor amines as indicated.) Doses above 2400 mg./day are not recommended.

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Dermatology

Porphyria

PORPHYRIA REFERS to a group of inborn errors of porphyrin metabolism manifested clinically by cutaneous photosensitivity and abdominal and neurological disorders. Ratner and Dobson,[1] in 1964, suspected that an aberration in purine metabolism may represent part of the defect in some cases of porphyria.

Classification

1. Erythropoietic porphyria:
   - A. Congenital photosensitive porphyria (Günther)
   - B. Erythropoietic protoporphyria
2. Hepatic porphyria (in this type the liver is the principal or only site of abnormal porphyrin formation):
   - A. Intermittent or acute type—with abdominal or nervous manifestations
   - B. Porphyria cutanea tarda—with photosensitivity, without other manifestations
   - C. Mixed type—photosensitivity with intermittent abdominal or nervous manifestations
   - D. Latent type—asymptomatic variations of porphyrin metabolism among relatives of those with manifest disease.

Erythropoietic Porphyria.

This is rare; it constitutes less than 1% of the cases. It is characterized by onset in early life, even shortly after birth. The urine is red and there is photosensitivity, with the formation of bullae on the exposed parts, especially the knees, ears, and hands. There may be linear scars around the mouth which give the face a puckered look. The skin is frequently hyperpigmented; moderate hypertrichosis of the face and extremities is common. The teeth are brown or brownish-red and fluoresce when exposed to ultraviolet light.

In erythropoietic porphyria the bone marrow contains large amounts of porphyrin (a mixture of uro-, copro-, and protoporphyrin). Circulating erythrocytes also contain excessive amounts of uro- and coproporphyrin; the spleen is rich in these substances.

Erythropoietic Protoporphyria

Redeker and Bronow[5] discussed this form of porphyria in 1964. They studied three patients with erythropoietic protoporphyria, the first to be reported in this country. There was elevation of protoporphyrin in the free erythrocytes and feces similar to the cases reported from Europe. The photocutaneous eruption in all three patients apparently resulted from excessive protoporphyrin in the plasma. The authors stated that the cutaneous features were those of hydroa aestivale; they proposed that hydroa aestivale is a form of erythropoietic protoporphyria. Their descriptions, however, suggested that the patients had solar dermatitis of the polymorphic type rather than true hydroa aestivale; edema, erythema, and eczematization were the principal

morphologic features. In the European cases there were recurrent episodes of urticaria following exposure to sunlight. In contrast to erythropoietic protoporphyria, the level of uroporphyrin rather than protoporphyrin is elevated in porphyria cutanea tarda.

Porphyria Cutanea Tarda

This disorder is of special interest because it is more common, constituting 30 to 40% of cases of cutaneous porphyria. It usually occurs between the ages of 30 and 60; occasional cases have been noted in childhood. The incidence in males is higher than in females.

The cardinal features are: (1) bullae, (2) hyper- and hypopigmentation, (3) hypertrichosis, and (4) eczematous or sclerodermoid plaques. Vesicles and bullae as large as 2.5 cm in diameter develop on the exposed parts, usually the face, neck, and hands, following exposure to sunlight or other types of trauma. These bullae occasionally become infected and crusted and may form deep ulcers. Healing is slow, with the formation of pigmented or depigmented, irregular, shallow scars. The exposed parts of the skin are violet or brown in color. Hypopigmentation may be diffuse or mottled and sometimes resembles vitiligo. Hypertrichosis occurs especially on the face and back. Yellow sclerodermoid plaques develop on the face, neck, back, or extremities of some of the patients. The urine is dark and fluoresces red when exposed to filtered ultraviolet radiation.

The epidemic of hepatic cutaneous porphyria in Turkey, caused by the ingestion of hexachlorbenzene, suggests that the disease may be totally acquired without an underlying hereditary metabolic defect.[2,3] Bleiberg and colleagues,[4] in 1964, reported porphyria cutanea tarda in 29 patients working in a chemical factory engaged in the manufacturing of 2, 4-dichlorphenol and 2, 4, 5-trichlorphenol substances which are used as weed killers and are apparently hepatotoxic.

Underlying Factors

Some patients who have porphyria cutanea tarda are chronic users of alcohol or barbiturates; other drugs, including chloroquine and antimalarials, are implicated in some cases. The life expectancy in porphyria cutanea tarda depends on the extent of progression of the associated liver disease. Biopsy of the liver or examination of the organ at necropsy may show varying degrees of fatty degeneration or cirrhosis. The organ also contains large amounts of uroporphyrin. In the hepatic forms of porphyria the amount of porphyrin in the bone marrow is normal.

Treatment

Treatment consists of a regimen to improve hepatic dysfunction and complications of liver disease. Alcohol and barbiturates should be avoided. The cutaneous lesions are benefited by avoidance of exposure to sunlight and trauma. Occasionally, corticosteroids produce improvement; a short course is indicated. If there is no benefit within a few days the drugs should be discontinued.

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Reprint requests to 538 Southdale Medical Building, Minneapolis, Minnesota 55435.
References may be secured from the author or the reprints.

A little impatience spoils great plans.—Culinary Almanac.

Clinical Path Conference

Uremia after Wilms's Tumor Therapy

A four-year-old white girl, residing on a farm near Duluth, had appeared to be completely well until March 31, 1968, when she fell in the barn. After this fall, she complained of pain in the right hip and, on April 5, of intermittent right knee pain. She was seen by her pediatrician in Duluth and was hospitalized at St. Mary's in Duluth on April 5, with working diagnoses of an abdominal mass, pain in the right hip (previous history of minimal fall) and a markedly elevated erythrocyte sedimentation rate.

First Admission

The first St. Mary's admission, from April 5 to April 19, 1968, yielded these positive findings: (1) a large, hard, nontender mass filling the left side of the abdomen; (2) an admission hemoglobin of 9.4 gm., a white blood cell count of 8,700 with a normal differential white blood cell study, normal platelets, and urine showing a specific gravity of 1.025 and negative chemically and microscopically; (3) negative x-ray studies of the hip, spine and chest. Films of the abdomen and an intravenous pyelogram disclosed a large extra-renal mass on the left.

Treatment during the first admission included: (1) On April 6, 1968, a left nephrectomy for Wilms's tumor. This was an uncomplicated excision, with no gross residual tumor remaining. The pathologic diagnosis was Wilms's tumor. (2) Beginning on the first postoperative day, April 7, actinomycin D (or dactinomycin)* was given intravenously, 1.0 mg. in five divided doses, on successive days. (3) On April 10, Co^{60} radiation therapy to the "tumor bed" was begun and continued on an outpatient basis after discharge from the hospital, so that by May 10 the child had received 3375 rads, midplane tissue dose. No complications arose during cobalt therapy and, at its completion, the patient's condition was reported as excellent; her appetite was good and she was gaining weight and remaining very active. No significant depression of white cells had occurred.

The child appeared to get along well until August 1968 when a rapidly growing right upper quadrant abdominal mass developed. The diagnostic findings on this admission to a medical center hospital on August 26, 1968, were: (1) Hepatomegaly (down 12 cm.) with a fist-sized nodule in the right upper quadrant of the abdomen. Two masses were seen in the liver area by liver scan. (2) X-rays of the spine, pelvis, skull, long bones and an intravenous pyelogram (right) yielded normal findings. A chest x-ray, however, showed multiple, bilateral pulmonary metastases. Treatment on this admission was (1) actinomycin D, 2.0 mg. total (0.015 mg./kg.) intravenously in five doses on successive days; and (2) simultaneously, CO^{60} 1500 rads to both lungs (11 days) and 2555 rads to the right upper quadrant of the abdomen and liver (16 days). During therapy, "substantial" shrinkage of the right upper quadrant mass was observed.

On November 4, 1968, her clinical progress was considered excellent; she was gaining weight; she had a good appetite and no problems. The liver was down 13 cm. but there was no tumor palpable in the abdomen. The lung metastases were no longer visible on a chest x-ray. Urinalysis was negative chemically and microscopically. No treatment was prescribed, but future treatment with actinomycin D was suggested every three months, the next treatment in December 1968.

Second Admission

From December 8 to 15, 1968, the child was in St. Mary's Hospital for "prophylactic" actinomycin D treatment. She was asymptomatic. Significant findings on this admission were: (1) Absence of lung metastases on a chest x-ray. (2) A hemoglobin of 9.4 gm., a white blood cell count of 14,000 with a differential white cell study that was normal except for 14% eosinophils. The platelets looked normal on a smear. The urine specific gravity was 1.013,

*Cosmegen Lyovac Powder—Merck Sharp & Dohme Products.

and it gave a 4+ reaction for protein, and microscopically showed a field packed with red blood cells. (3) Physical examination showed the liver down 1 cm.; there was no palpable tumor. Actinomycin D, total 1.1 mg., was given intravenously in five doses on successive days.

Third Admission

After her discharge from St. Mary's Hospital in Duluth on December 15, the child got along very well at home; she was active, playing, and had no complaints until January 16, 1969, when she vomited once, but then had no further symptoms until the night of January 19, when she began to cough, breathed rapidly, and became listless and dyspneic. On January 20, 1969, she was admitted to St. Mary's Hospital. She was very pale, and only a few rales and rhonchi were audible in the lungs. All other physical findings were normal. Laboratory data showed an initial hemoglobin of 4.8 grams, a white blood cell count of 8,150 with 2% nonsegmented neutrophils, 81% segmented neutrophils, 14% lymphocytes, 2% monocytes and 1% basophils. The urine specific gravity was 1.014; the urine gave a 3+ protein reaction and microscopically showed six to eight white blood cells per high field and 75 to 80 red blood cells. Serum sodium was 140 mEq/L, potassium 4.8 mEq/L, chlorides 114 mEq/L; carbon dioxide combining power was 13 mEq/L. The venous blood pH was 7.27, the pCO_2 32 mm. Hg., and the HCO_3 14 mEq/L. Diffuse, bilateral pulmonary infiltrates were seen on a chest x-ray. The patient had a nonproductive cough, a respiratory rate which rose as high as 90/minute, a pulse rate which rose as high as 120/minute, and a temperature of 100.4° (R).

A 360-cc. blood transfusion raised the hemoglobin level to 8 gm. Sodium bicarbonate was given intravenously without effect on the blood pH. Ampicillin was administered intravenously; the temperature decreased from 100.4° to 99.4° (R). The child's symptoms persisted unchanged. She had a normal stool but there was no spontaneous voiding. Catheterization yielded 115 cc. of urine having a specific gravity of 1.016, giving a 4+ reaction for protein, and microscopically showing an occasional white cell and 15-20 red blood cells per high-power field, as well as 4-6 granular casts. On the morning of January 21, the second hospital day, the blood urea nitrogen was 72 milligrams percent. The respiratory rate remained high, and respiratory efforts became grunting. Late in the afternoon coffee-ground emeses occurred and shortly thereafter the patient died.

Discussion

Dr. A. C. Aufderheide:

In summary, this child had a Wilms's tumor treated with surgical excision, radiation therapy and actinomycin D in the manner currently in use. Her response was gratifying, but an unanticipated fulminating uremia terminated her life six days after the onset of symptoms, on the second hospital day of her last St. Mary's admission. The emphasis in this diagnostic problem presentation has not been upon a differential diagnosis of abdominal tumors in childhood, etc., pointing to the diagnosis of a Wilms's tumor, but rather upon the postoperative course and the problem presented by the unanticipated terminal events.

Dr. J. E. Kwako:*

This four-year-old girl's Wilms's tumor was treated with all three modalities available: surgery, radiation and chemotherapy. The treatment was carried out much as is generally advised. The final episode was one of acute uremia with a terminal pulmonary complication. The etiology of the uremic condition could be one of three things:

Unrelated Kidney Condition

There is no clinical reason to suspect some unrelated kidney condition, and the temporal relationship is such that I would prefer to relate the uremia to Wilms's tumor or its treatment.

*Pediatric Department, Duluth Clinic, Duluth, Minnesota.

Natural Course of Wilms's Tumor

Wilms's tumor could be present in the remaining right kidney. Bilateral Wilms's tumor has been reported in different series, the incidence varying from one to ten per cent[1]. Of course, the original tumor could also metastasize to the remaining kidney or its outflow tract. Against the etiologic factor for the uremia being the tumor itself are: the isotopic liver scan demonstration that the right upper quadrant masses were intrahepatic; the normal-appearing right kidney on intravenous pyelography; the absence of a palpable abdominal mass on the last admission.

Complications of Treatment

If uremia is to be related to treatment, consideration must be given to the roles of actinomycin D and radiation. The literature does not record serious nephrotoxicity due to actinomycin D itself and, when the manufacturer of the drug was questioned, he reported no record of serious nephrotoxicity due to it.

However, medical precedent has been established for renal damage from ionizing radiation. Whereas in earlier years the kidney was thought to be resistant to radiation effect, more recently this attitude has been modified. Experimentally, tubular atrophy and renal fibrosis were produced in rabbits and dogs with dosages in the range of 2,000 rads.[2] Radiation therapy of bilateral Wilms's tumor has been a source of information for the effect on human kidneys; dosages above 2,500 rads over a five-week period were found to be associated with renal damage.[3] Symptoms in these instances included lassitude, headache, dyspnea, anemia, albuminuria, and congestive heart failure, with death occurring in uremia. Acute and chronic forms of reaction have been described, often with the development of hypertension.

A significant clinical feature, also apparent in the experimental animal studies, appears in the latent interval between radiation therapy and the onset of symptoms. This interval apparently varies from six to 18 months.

In our patient, 2550 rads were delivered to the right side of the abdomen (and presumably to the right kidney) in August 1968, together with concurrent actinomycin D therapy. Four months later, at the time of prophylactic actinomycin D therapy, four plus proteinuria and microscopic hematuria were demonstrated, and one month later the patient had similar urinary abnormalities with frank uremia. Unfortunately blood pressure measurements were not made. These laboratory findings, as well as the time interval, are consistent with renal radiation toxicity. The pulmonary problem can be accepted as a uremic complication.

I believe this child died from radiation nephritis.

Chemotherapy

Another aspect of this presentation should be mentioned. The dramatic therapeutic response of the pulmonary metastases, documented on the x-ray studies, should encourage us to adopt a far more aggressive attitude toward this tumor than has been customary in the past. Justification for such optimism comes from several areas. Australian experience records a rise from 11 to 62 per cent five-year-survival rates since the addition of actinomycin D to their therapeutic regimen.[4] Farber et al. from Boston found a gradual rise in survival rates since 1914, with a precipitous rise since 1957, when the use of actinomycin D was instituted.[5]

General agreement on dosage is noted in the literature and is in the range given to this child. There is some variation in opinion about the timing of therapy. Therapists at the Mayo Clinic, for example, believe it is important to start therapy as soon as possible, and the actinomycin D is usually administered while the patient is in the operating room; radiation therapy is likewise begun promptly—the patient sometimes receiving his first treatment upon his departure from the surgery suite to his room.[6] Others are less compulsive about the immediacy.[7] Krivitt and others reviewed the results of early and delayed treatment and believed their study provided strong support for the value of early treatment.[7] The virtue of multiple doses over several days, rather than a single dose, has also been demonstrated.

Prophylactic courses of therapy are advised at about three-month intervals for the first several years after operation, as was done in the patient here presented. Many workers are of the opinion that the appearance of metastases should stimulate aggressive repetition of all forms of therapy deemed appropriate rather than the assumption of an attitude of despair. Actinomycin D is toxic. Immediate reactions include gastrointestinal and dermatologic problems, as well as pancytopenia. Delayed reactions may be alopecia, abdominal pain, fever, leukopenia and thrombocytopenia. I found no reference to nephrotoxicity.

Clinical Diagnosis

1. Radiation Nephritis

Dr. Aufderheide:

The immediate cause of death was massive, bilateral, diffuse pulmonary hemorrhage. Fifteen white pulmonary metastatic nodules, varying from 1 to 5 mm. in diameter, were scattered through both lungs in a subpleural position. The former site of the metastatic nodules in the liver was represented by two small (1 cm.) necrotic areas within which no tumor could be demonstrated. A partially necrotic lymph node in the porta hepatis contained tumor. Histologically all tumor had the structure of Wilms's tumor, identical with that originally present in the left kidney. No other tumor was found.

The remaining (right) kidney weighed 73 grams and was normal grossly, as were the ureter and bladder. Renal histology demonstrated widespread, acute, necrotizing arteriolitis, especially involving afferent arterioles. Stages were represented varying from focal, intramural hyaline necrosis to total necrosis of the entire wall with lumen thrombosis. Glomerular changes appeared to be secondary to the vascular phenomena and consisted of findings all the way from simple capillary thrombosis to frank infarction. Modest tubular atrophy testified to the fact that the process had been in progress for at least several months. These findings are indistinguishable from the type of pathology expected in the adult form of "malignant hypertension" with the development of acute uremia, a change pathologists often term "renal arteriolar thrombonecrosis."

Because of the microangiopathy, as well as the arteriolar and glomerular thrombosis, together with serious clinical hemorrhage, we suspected the syndrome of consumptive coagulopathy. No coagulation studies were performed antemortem. After death, the only source of evidence for this suspicion lay in the admission peripheral blood smear. Re-examination of this smear demonstrated the presence of extensive schizocytosis with erythrocyte fragmentation and many "helmet" cells.

Dr. Mostofi of the Armed Forces Institute of Pathology, who has concerned himself with this problem,[8] kindly reviewed the renal histology in this patient and agreed with the diagnosis of "radiation nephritis."

Necropsy Diagnoses

Radiation nephritis.
Metastatic Wilms's tumor to abdominal lymph nodes and to both lungs.
Possible acute hemolytic uremic syndrome.

Since radiation dosage up to 2500 rads to a kidney has been considered to be within appropriately safe limits in the past, Dr. Asta has been kind enough to review the therapy administered to this patient.

Dr. J. J. Asta:*

The potentiating effect of actinomycin D on ionizing radiation was not appreciated prior to the advent of the use of this drug in the treatment of Wilms's tumor. Since this fact has become apparent, radiologists have been aware that they must reconsider radiation dosages for various tumor entities for which actinomycin D is used, so that allowance may be made for the radiation-sensitizing effect of the drug. Dr. D'Angio's work[9] stimulated the reduction of radiation dosage by 25 per cent in patients receiving actinomycin D for Wilms's tumor. This would imply that maximal radiation to the unaffected kidney should be reduced from 2500 rads to about 1700 rads or less.[10]

The Boston group headed by Dr. Gross[11] has reviewed 200 cases of Wilms's tumor and divided the survival rates into periods of time. From 1914 through 1930, the survival rate was 15 per cent; in the 1930s, it was 32 per cent; in the 1940s, with the advent of radiation therapy, it was pushed up to 47 per cent, and, since 1957, at which time actinomycin D was used at the urging of Dr. Farber,[12] the survival rate has risen to nearly 80 per cent.

Why is the Boston group's recent survival rate so encouraging? I think this team has certain basic criteria to which they almost invariably adhere.[13] Their approach is: (1) Prompt nephrectomy (preferably on the day of admission). (2) Immediate preoperative use of actinomycin D in all cases, regardless of whether or not a shower of metastases is suspected. (3) The use of actinomycin D plus radiation. This is begun on the way back from the operating room. (4) Actinomycin D is used during the period of greatest risk, which is assumed to be the first nine months after the diagnosis has been made. (5) Their approach is rather vigorous; if the patient shows recurrences, they do not hesitate to repeat the first three steps. Based on these steps, their survival rates have been exceedingly good. Others[14] have had similar results and all have concluded that the addition of actinomycin D has perhaps produced the most marked improvement of all forms of therapy in the survival rates of patients with Wilms's tumor.

Dr. Aufderheide:

It is remarkable that actinomycin D will amplify the toxicity even of *previously* administered radiation.

The complications presented by this patient and outlined by our discussers clearly define the need to adjust radiation dosage when actinomycin D is also administered.

*Department of Pathology, St. Mary's Hospital, Duluth, Minnesota 55805.

Final Anatomic Diagnoses

Radiation nephritis.
Metastatic Wilms's tumor to abdominal lymph nodes and to both lungs.
Possible acute hemolytic uremic syndrome.

A. C. Aufderheide, M.D.*
Duluth, Minnesota

*Department of Radiology, St. Mary's Hospital, Duluth, Minnesota.

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Henry A. Troy, M.D.

During his vacation, Dr. Henry A. Troy and his wife spent some time in the Black Forest and while revisiting the top of the Feldberg (its highest peak), he was fascinated by the rich meadows seen against a colorful sky, with lively cloud formations over this old wire fence. He made a quick sketch and when he returned home, started the painting shown on the cover of this issue.

Practicing in Oceanside, New York, Dr. Troy has always been interested in art and showed aptitude in this direction even at the age of 10 years. However, he decided to study medicine, and art was set aside. He graduated from the University of Berlin in 1923 and became an instructor in surgery. In 1938 he came to the United States and in 1943 resumed painting while on vacation. He has painted ever since and has won several first and second prizes at the American Physician's Art Association exhibitions and a first prize at the New York State Academy of General Practitioners Art Exhibit.

Men occasionally stumble over the truth, but most of them pick themselves up and hurry off as if nothing had happened.—Winston Churchill

Vaccination is the medical sacrament corresponding to baptism.—Samuel Butler

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acne
amebiasis
anthrax
bacillary dysentery
bartonellosis
bronchitis
bronchopulmonary infection
brucellosis
chancroid
diphtheria
endocarditis
genitourinary infections
gonorrhea
granuloma inguinale
listeriosis
lymphogranuloma
mixed bacterial infection
osteomyelitis
otitis
pertussis
pharyngitis
pneumonia
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Laboratory Medicine

Pregnancy Tests*

THE ANCIENT EGYPTIANS performed the first pregnancy tests.[1] They noted that certain plants bloomed more quickly when watered with urine from pregnant women; something in the urine stimulated plants to grow and seeds to germinate, indicating a positive pregnancy test.

In 1927, Aschheim and Zondek introduced the first specific and reliable pregnancy test. They injected the patient's detoxified urine into an immature female mouse. Four to five days later, they examined the ovaries. The presence of corpora lutea indicated a positive presumptive test for pregnancy.

In the early 1960s, immunoassays were developed that were fast, simple, and convenient. In the last few years, yet another technique, radioimmunoassay, has been introduced. Though still available primarily on a research basis, it is capable of precisely measuring minute amounts of gonadotrophic hormone. Other laboratory tests intermittently proposed for diagnosing pregnancy include urinary histidine, estrogens, and progesterones, as well as leukocyte alkaline phosphatase, placental alkaline phosphatase isoenzyme activity,[2] and cysteine aminopeptidase activity.[3] None are as sensitive or as specific for pregnancy as the now standard methods based on determining human chorionic gonadotrophin in the urine.

Human Chorionic Gonadotrophin Levels in Pregnancy

International Units

Human chorionic gonadotrophin is expressed in terms of international units of gonadotrophic activity. One international unit (I.U.) is defined as the specific gonadotrophic activity of 0.1 milligrams of dried standard at the National Institute of Medical Research in London. This amount is capable of producing maturation of the vaginal epithelium in an immature rat.

During the menstrual cycle the urinary excretion of pituitary gonadotrophic hormone is at its peak (0.1-4.1 I.U./ml.) during the time of ovulation.[4] In pregnancy, however, urinary and serum human chorionic gonadotrophin levels rise progressively and rapidly within 48 hours after the fertilized ovum implants. Human chorionic gonadotrophin levels peak between the 50th and 90th day following the onset of the last menstrual period, with urine and serum levels ranging between 50-120 I.U./ml. During the 2nd and 3rd trimester, when the placenta takes over estrogen and progesterone production, the human urine chorionic gonadotrophin levels plateau at about 10-20 I.U./ml. After delivery, levels fall and should be normal by the 10th post-partum day.[5]

Pregnancy tests, in fact, represent various methods of detecting human chorionic gonadotrophin in urine or serum. The ideal pregnancy test should combine specificity and sensitivity. Specificity connotes absence of cross reactivity or interference with other metabolic substances (e.g., hormones or drugs). Sensitivity reflects the minimal levels of human chorionic gonadotrophin necessary to produce a positive pregnancy test. In early pregnancy (34-40 days from the last menstrual period) human chorionic gonadotrophin levels are low (0.5-2.0 I.U./ml). Only the most sensitive tests will give positive results. Less sensitive tests, capable of detecting 3.5 I.U./ml. or more, may first become positive between 40-50 days. Between 50-90 days, due to peak human chorionic gonadotrophin levels, even the most insensitive tests will yield positive results.

Biological Pregnancy Tests

In biological pregnancy tests,[7] detoxified urine is injected into laboratory animals. Various morphologic or biochemical changes indicate whether the test is positive or negative. The end points include corpus luteum formation, ovarian hyperemia, ovulation, spermeation,

*See editorial page 273.

increase in uterine or prostatic weight, and depletion of ovarian cholesterol or ascorbic acid content. These human chorionic gonadotrophin biological assays are 96-99 percent accurate. They are, however, time-consuming, expensive, and subject to technical problems. Animal care and breeding as well as detoxified urine are necessary. Furthermore, drugs can produce both false positive and false negative pregnancy tests by altering the recipient animal's metabolism.[6] The classical Aschheim-Zondek and Friedman tests using immature mice and rabbits are accurate and sensitive but too time-consuming for practical use. In the insensitive Hogben method using the female toad (Xenopus laevis), urine must be concentrated prior to animal injection. The Frank-Berman method, using ovarian hyperemia in immature mice, is sensitive and accurate and can be used for quantitation.

Immunoassays

Immunoassays detect human chorionic gonadotrophin excreted in the urine and are based on antigen-antibody reactions. The hemagglutination and latex particle agglutination tests are rapid, sensitive, inexpensive, and easy to use.

Indirect Agglutination Tests

In the indirect agglutination tests the antigen is human chorionic gonadotrophin and the antibody is an anti-serum obtained from animals (usually rabbits) immunized against human chorionic gonadotrophin. Carrier vehicles, such as red blood cells or latex particles, previously coated or sensitized with human chorionic gonadotrophin will agglutinate when mixed with rabbit anti-human chorionic gonadotrophin sera. If the anti-serum is previously mixed with a pregnant woman's urine containing human chorionic gonadotrophin, the anti-human chorionic gonadotrophin serum is neutralized and hence will not agglutinate human chorionic gonadotrophin-sensitized carrier particles. *Lack of agglutination implies a positive pregnancy test.* The anti-human chorionic gonadotrophin sera will not be neutralized when mixed with urine of non-pregnant women containing no detectable human chorionic gonadotrophin. Thus, uncombined anti-human chorionic gonadotrophin sera will be free to agglutinate with human chorionic gonadotrophin-sensitized particles, with *agglutination implying a negative pregnancy test.*

Tube Tests

The table lists the commonly used immunoassays for human chorionic gonadotrophin. Test tube methods requiring an incubation time of two hours include the U.C.G. (urinary chorionic gonadotrophin)*[8] and Pregnosticon†[9] tests. These are hemagglutination tests that use red blood cells as carriers for human chorionic gonadotrophin[4] and are the most sensitive agglutination immunoassays now available. They are capable of detecting chorionic gonadotrophin in the urine in a concentration of 0.7-1.0 I.U./ml. Following time-consuming extraction procedures, both of these tube tests can be adapted for use with serum.

Slide Tests

Slide tests, in contrast, can be performed in minutes. The Gravindex‡ and Pregnosticon slide tests use latex particles as human chorionic gonadotrophin carriers. Although rapid and simple to do, they lack the sensitivity of the tube methods. The reliable Gravindex test still gives occasional false positive results with massive proteinuria and hematuria.[6] The Gravindex as well as Pregnosticon slide tests may be negative in early pregnancy up to 15 days after the first missed menses.

Direct Agglutination Test

A recently available direct agglutination test for pregnancy is the one-stage test. Latex particles are sensitized or coated with an *antibody* to human chorionic gonadotrophin, and the antibody-sensitized latex particles are mixed with patient serum or urine on a glass slide. If enough human chorionic gonadotrophin is present in sufficient concentration, latex particles will agglutinate, indicating positivity. The absence of human chorionic gonadotrophin activity is indicated by lack of agglutination, implying negativity. This test is claimed to be accurate, sensitive and free from interference from urine protein or hemoglobin; further-

*Wampole Laboratories, Stamford, Connecticut.
†Organon, Incorporated, West Orange, New Jersey.
‡Ortho Diagnostics, Raritan, New Jersey.

more, it is claimed that in those cases where it is not feasible to obtain a urine specimen, the test can be performed on serum or plasma without time-consuming extraction procedures.[12] Comparative studies with other established pregnancy tests are needed to verify these claims and are currently under way in our laboratory.

False Positive Pregnancy Tests

Biological Factors

Many biological and technical factors influence immunological methods and can result in false positive or false negative results.[13] With proteinuria in excess of 1.0 grams per 24 hours or grossly bloody urine, false positive slide tests can occur. Cross reactivity between human chorionic gonadotrophin and the pituitary gonadotrophic hormones, especially in the post-menopausal state, can give false positive tests, particularly with the highly sensitive urinary chorionic gonadotrophin (U.C.G.) and Pregnosticon tube methods.[4] In post-menopausal women as well as in normal males, urine pituitary gonadotrophin levels may be present up to 0.40 I.U./ml.[14]

Neoplasms

Positive urine tests are also reported with choriocarcinoma in the male, ovarian teratomas,[6] persistent corpus luteal cysts, and undifferentiated lung carcinomas.[16] In the latter situation the neoplasm elaborates a hormonal substance with gonadotrophic activity. These "gonadotrophin-producing carcinomas" of the lung are associated with gynecomastia and a long smoking history. Large quantities of this gonadotrophin are present in the patient's urine as well as in homogenates of the neoplasm and its metastases.[17]

False Negative Tests

False negative tests can occur when urine is stored for prolonged periods at room temperature or even at 4° C.[4] Dilute urine with specific gravity less than 1.015, especially when taken earlier than the 40th day of pregnancy, may be negative, whereas a more concentrated early morning specimen may be positive.[13] Because of an associated drop in human chorionic gonadotrophin titer in ectopic pregnancies[18] and threatened abortions,[19] false negative pregnancy tests are not uncommon. In these low titer situations, rapid slide methods may fail to detect human chorionic gonadotrophin and the two-hour highly sensitive tube methods are clearly indicated.

A positive pregnancy test performed in clinically suspected threatened abortion implies

*Wampole Laboratories, Stamford, Connecticut.

TABLE

Characteristics of Commonly Used Tube and Slide Agglutination Pregnancy Tests

	Agglutination Technique	Carrier For HCG	Sensitivity Peak† (I.U./ml.)	Serum Adapted	
Pregnosticon (Organon, Inc.) Tube	Indirect	RCB's	0.65-0.8 I.U.	Yes	Valuable in (1) low titers (2) well tested
U.C.G. (Wampole Labs) Tube	Indirect	RBC's	1.0 I.U.	Yes	(1) Used undiluted gives 0.3 I.U. sensitivity (2) Valuable in low titers
Gravindex (Ortho-Diagnostics) Slide	Indirect	Latex Particles	3.5 I.U.	No	(1) Affected by Alb, Hgb
Pregnosticon (Organon, Inc.) Slide	Indirect	Latex Particles	1.0-2.0 I.U.	No	(1) Sensitive (2) less Alb, Hgb interference
D.A.P. (Wampole Labs) Slide	Direct	Latex* Particles	2.0 I.U.	Yes	(1) Scanty testing (2) Prozone effect in over 200 I.U./ml. (3) Not affected by Alb, Hgb

*Sensitized with anti-HCG
†Manufacturer's specifications

persisting placental function. A negative test usually heralds an unsuccessful outcome for the pregnancy. Yahia, however, has reported seven cases of threatened abortions with negative pregnancy tests who went on to deliver viable fetuses.[20] False negative pregnancy tests have also been reported in the third trimester when human chorionic gonadotrophin levels are lower than those seen between 50-90 days.

Pregnancy Testing in Trophoblastic Disease

High titers of human chorionic gonadotrophin present in the serum or urine after the first 90 days of pregnancy constitute strong evidence for the clinical diagnosis of trophoblastic disease.[21] Pitfalls in this diagnosis include elevated levels due to twin pregnancies or polyhydramnios. Titers done prior to 90 days are generally non-diagnostic, but are helpful in that very low titers exclude the diagnosis and equivocal titers can be used as baselines for further studies.

In trophoblastic disease, serial bioassays have remained the classical means of following therapy.[22] Recently, however, with the improvement in sensitivity and technical ease of the tube immunoassays,[4] the trend has been away from the bioassays.[23] When the usual tube pregnancy test is negative and there are still grounds for suspecting trophoblastic tumor, urine must be further concentrated so that lower human chorionic gonadotrophin levels can be detected.[24] The urine is concentrated by acetone precipitation with a resultant ten to one hundred-fold increase in sensitivity, allowing for precise quantitation of low levels of human chorionic gonadotrophin.[25] Whether a sensitive bioassay or a tube immunoassay is performed, quantitation is necessary since a rising or falling titer may be helpful in dictating subsequent therapy.[26] These patients should be followed for at least three years with monthly quantitative pregnancy tests during the first six months. The patient should not be considered in remission until urinary gonadotrophin activity is within the normal range of pituitary activity.[24] The comparatively complex radioimmunoassay has recently shown promise in the detection of low levels of human chorionic gonadotrophin.[24] At present, however, it is neither widely available nor feasible in most laboratories.

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Melvin Sinykin, M.D.*
Minneapolis, Minnesota

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A Ship at Sea

Truly each new book is as a ship that bears us away from the fixity of our limitations into the movement and splendor of life's infinite ocean—Helen Keller.

Didactic

Acute Purulent Meningitis*

GEORGE C. FLORA, M.D.
Minneapolis, Minnesota

THE CLINICAL entity of acute purulent meningitis is medically spectacular and causes little difficulty in diagnosis. The sudden departure from a usual state of health to gross debility with fever, cephalgia, somnolence† and delirium in one to three days with signs of stiff neck is pathognomonic. The confirmation of the diagnosis by lumbar puncture and examination of the cerebrospinal fluid for pleocytosis is a simple procedure for most medical practitioners. Bacteriology laboratories can readily identify the causative organism and its sensitivity to antibiotics. The scientific handling of this disorder is one of the best in all of medicine. Acute purulent meningitis, regardless of etiology, produces the same general symptoms and signs. The initial symptom is invariably headache, which is in no way pathognomonic. It is usually most intense and progressive over 12 to 24 hours, becoming excruciating and is unrelieved by usual anodynes.

Physical Examination

Meningeal Irritation

The initial signs of meningitis are due to meningeal irritation, the most consistent being "stiff neck," varying from the subjective "tightness" to absolute immobilization by muscle guarding. The muscular splinting is seldom localized to the cervical region but rather is diffuse throughout the paravertebral muscle mass, resulting in spine "stiffness" reflected by the typical "tripod" posturing of the meningitis victim as he attempts to sit. The tripod phenomenon is weight bearing on the two dorsally extended outstretched hands and the buttocks, with impaired ability to flex at the waist. The "muscle guarding" or "hyper-irritability" extends to the extremities; the Brudzinski sign which results in flexion at the knees on attempting to flex the neck, and Kernig's sign which results in decreased ability to extend the knee when the thigh is flexed on the abdomen are examples.

Fever

Fever is invariably present and may reach 108-109°. Both early therapy and advanced age have a tendency to moderate the fever, but it is present to some degree in all victims. Meningitis is associated with some pathological involvement of the brain parenchyma. Pathologically it is actually a meningoencephalitis and will show some diffuse cerebral deficit. Somnolence, lethargy, disorientation, delirium or coma is common and of great clinical importance.

*Presented at Neurology Continuation Course on Neurological Emergencies. Associate Professor of Neurology, University of Minnesota Medical School, Minneapolis, Minnesota.
†See Test Your Word Score, Page 277.

Laboratory Studies

Laboratory signs are found in the cerebral spinal fluid examination; this will show a pleocytosis of considerable numbers. The cell count, composed chiefly of polymorphonuclear cells, is expected to range in the hundreds or thousands with an associated increase in cerebrospinal fluid pressure and protein.

The Organisms

Meningitis which one deals with clinically is limited to five varieties; the meningococcal, the pneumococcal, the streptococcal, the hemophilus influenzal and the staphylococcal. Remarks concerning our concepts of these five may be useful.

Clinical Manifestations

Meningococcal Meningitis

Meningococcal meningitis appears sporadically and in epidemics and involves primarily the younger age groups during the winter and spring seasons. Outbreaks occur where groups of young people are brought together from diverse localities in service training camps, college dormitories and other "living together" situations.

The initial manifestation is a nasopharyngitis followed by a septicemia which produces a profound systemic response with signs of fever, apathy and prostration. These young people look extremely ill very early. A petechial or purpuric rash which may be seen on the trunk and limbs is quite diagnostic. The lumbar puncture in these cases will reveal the gram-positive cocci which will be sensitive to numerous antibiotics. The drug of choice at this time remains penicillin in doses of 20 million units intravenously per day. A newer antibiotic, Keflin, in doses of 12 gm. per day, is also reported to be effective. Therapy is very good and should be continued for at least ten days.

Pneumococcal Meningitis

Pneumococcal meningitis is a secondary form of meningitis seeding to the meninges from infections of the sinuses or the middle ear, or as complications of skull fractures. It occasionally follows surgical procedures on the nose and throat. The ages most frequently affected are those at the two extremes, the very young and the very old, with "peak" reports in the first and fifth decades. The course is not unique. The cerebrospinal fluid will reveal gram-positive diplococci which are sensitive to penicillin in doses of 20 million units intravenously per day. Amphicillin (Omnipen) and sodium cephalothin (Keflin) are both proving to be very effective in the control of this meningitis.

Streptococcal Meningitis

Streptococcal meningitis is another secondary form of meningitis which is frequently seen in patients with otitis media or severe sinus infections. Streptococcal infections of the skin of the face may also seed into the meninges. Streptococcal meningitis occurs in bacterial endocarditis, and less frequently this form of meningitis is seen as a complication of surgery of the nose, nasal

sinuses or the skull itself. The present treatment is penicillin in doses of 50 to 100 million units, intravenously daily. Again both Amphicillin and cephalothin are proving effective.

Influenzal Meningitis

Influenzal meningitis is the most common form of meningitis seen in infancy and early childhood, especially during the first two years of life. This is a neurophilic or primary meningitis of children. It occasionally is seen in the adult secondary to an acute sinusitis, otitis media or skull fracture. In childhood it is frequently associated with an initial gastroenteritis quickly followed by hyper-irritability, somnolence with fever, stiff neck and bulging fontanelles. The cerebrospinal fluid in these cases is cloudy, with increased pressure, and contains polymorphonuclear cells by the thousands. The organism appears as a gram-negative bacillus which is sensitive to chloramphenicol in doses of 50 mg. per kg. daily. Both Amphicillin and cephalothin are proving effective in this form of meningitis and may become the drugs of choice.

This particular form of meningitis has a predilection to form meningeal adhesions and results in chronic increased intracranial pressure causing mental retardation especially in the inadequately treated or in cases where there has been delayed therapy. Subdural effusions are also a frequent complication which one must be alert to; after an initial response to therapy there develop signs of added cerebral insult. If persistent vomiting, increasing fever, bulging fontanelles or seizures develop, an effusion is indicated, and early and adequate drainage is mandatory.

Staphylococcal Meningitis

Staphylococcal meningitis has become relatively more common as the antibiotic-resistant staph strains have increased in prevalence. This form of meningitis which is usually of the aureus strain is invariably secondary from a cellulitis of the skin, carbunculosis or osteomyelitis. These patients are usually systemically ill, and one must be alert to the early signs of meningitis. The cerebrospinal fluid will grow out the invading organism which may well have developed in sensitivity to the present drug of choice which is penicillin. Penicillin dosages of 50-100 million units intravenously and daily have been most successful. Methicillin (Staphcillin) is utilized in cases which show resistance to penicillin. Keflin is showing promise as being a most effective agent in the treatment of staphylococcal meningitis.

These clinical entities are the prevalent forms and they are the ones which you will be treating in the practice of medicine. Familiarity with their characteristics and their therapies is simple and most useful.

Language

The most unfortunate letter in the alphabet, some say, is the letter "e" because it is always out of "cash," forever in "debt," and never out of "danger."

That is true. Still, it's never in "war," always in "peace," and always in something to "eat." It is the beginning of "existence," the commencement of "ease," and the end of "trouble."

Our grand business is not to see what lies dimly in the distance, but to do what lies clearly at hand.—Carlyle.

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SHENANDOAH, JULY 16. Roger Sherman of Waynesboro suffered head lacerations but escaped serious injury when the tractor-trailer he was driving skidded on Deep Run Bridge and jackknifed. It took rescue workers thirty minutes to remove him from the cab which was dangling over the edge of the bridge. Sherman is resting comfortably in University Hospital where his condition is listed as satisfactory.

Frankhouser called my attenti

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Grand Rounds

Effect of Air Pollution from Fossil Fuel Combustion on Human Health

ARNOLD W. LINDALL, M.D., Ph.D.
Minneapolis, Minnesota

AN AWARENESS of the problems of air pollution has arisen within the past few years. In November 1966, a report of a governor's committee on air resources was made to the Minnesota Legislature,[1] wherein it was documented that air pollution monitoring was inadequate in Minnesota and not enough figures were available to even set trends for gaseous emissions. It would seem unlikely that a complete evaluation is available even now.

Quantitative Factors in Coal Burning

Fossil fuels used in Minnesota power facilities in 1964 were considered the equivalent of 31×10^6 tons of coal per year.[1] The recently-built Allen S. King generating plant on the St. Croix River was expected to burn 2×10^6 tons of coal per year, which is 1/15 of the total fossil fuels in 1964.[2] Such a plant, burning coal with 3% sulfur content would produce 1.14×10^5 tons of sulfur dioxide (SO_2) per year or 312 tons per day. If all of this SO_2 were converted to sulfuric acid, there would be 1.4×10^6 liters of such acid produced per day by the King plant. Estimates of SO_2 concentration in air contributed by this plant were made by Raymond Wanta, a meteorologist, who found that the SO_2 concentration would be 0.43 parts per million for two one-half-hour periods a year (based on a 500 foot stack) at distances of 2.5 miles from the source.[3] I did not see any reference to the effect of rain on the deposition of SO_2. In further testimony, during the King plant hearings, Louis McCabe

*Presented as a Medical Grand Rounds at Hennepin County General Hospital, January 21, 1969.

stated in reference to air quality standards which he considered to be too rigid:[4]

> "For example, Dade County, Florida, has a regulation that sulfur dioxide shall not exceed 0.1 part per million at ground level as an 8-hour average and 1 part per million average for one hour. This is unreasonable in the light of present knowledge."

A physician, Dr. Machle, testifying for Northern States Power, stated that we must accept a "certain amount of sulfur dioxide in our atmosphere as an inevitable part of every-day life,"[5] He also said:

> "My own studies in industry, the community, and in large studies where I have advised and participated have revealed no direct evidence that levels of sulfur dioxide anywhere near those found in urban atmospheres are a direct and sole cause of illness."

To paraphrase his testimony further: the non-specific irritation effects occur at concentrations of 5 parts per million and above, and the effects from 5 to 8 parts per million are transitory. He also found that only 5% of the people can taste or smell 1 part per million.

The foregoing information is taken to represent the professional attitude of the power industry in Minnesota in 1965 and will be contrasted with the prevailing medical research.

Components of Air Contamination

In the report of the Governor's committee some of the elements of pollution include:

Particulate contaminants
- Soil whipped up by wind
- Soot with absorbed hydrocarbons
- Industrial dusts from sanding, grinding, milling, etc.
- Street refuse

Gases and vapors
- CO_2 — of little immediate health significance
- CO — reaching high levels in traffic
- SO_2 — from burning coal; forming SO_3 and readily soluble in water to form H_2SO_4
- NO —
- NO_2 — both compounds found in urban air. NO_2 is highly toxic.
- Organics — possible carcinogens

Photochemical smog
- PAN — peroxyacetyl nitrate
- Ozone — causing changes in lungs at low concentrations
- Aerosoles — undefined

In 1963 the American Medical Association advised the physician:[6] In particulate smogs the ratio of organic to total suspended particulates is the best indicator of pollution. These are principally benzene-soluble materials. They also suggest that SO_2 values in excess of 0.2 parts per million (a value said to injure plants after eight hours) should be considered undesirable. Values of 5.0 parts per million can be considered serious (producing bronchoconstriction).

Epidemiological Studies of the Effect of Pollution on Humans

Effect of SO_2

We should now recall Dr. Machle's statement claiming that there is no evidence relating direct effects of SO_2 to injury in humans. Such evidence has been very difficult to obtain since high-risk humans cannot be subjected to laboratory experimentation. It must be noted that for many years the tobacco industry denied the effect of smoking on lung cancer and heart disease, a relationship that almost all physicians now accept. The evidence on the toxic effects of air pollution is beginning to appear from careful statistical studies and medical measurements, in the same way as the evidence regarding smoking was obtained.

The pH of Rain

In 1958 Gorham found a significant correlation of local deaths due to bronchitis in England and the pH of rain in a particular area[7] which was in a direct wind line from the industrial centers. Total sulfate deposits did not correlate well with bronchitis. In another study, however, pneumonia deaths correlated strongly with atmosphere sulfate deposition.[8] These differences may be related to aerosol characterictics, in that SO_2 may reach the deeper respiratory zones.

Sulfur Dioxide vs. Disease

A very important epidemiological study, done by Sterling et al.[9] in classifying admission diseases as highly relevant, relevant, and irrelevant to pollution data, found that the highly relevant category included allergic disease, eye inflammations, acute respiratory disease and bronchitis. The other classifications were less and less related to the respiratory system. Chronic lung disease would be considered as a relevant disease. High correlations were observed between all measured pollutants and admissions for highly relevant disease. For relevant disease all pollutants were significant except carbon monoxide, nitrous oxide, total oxides of nitrogen, oxidant precursors and particulates. For irrelevant disease all correlations were negative.

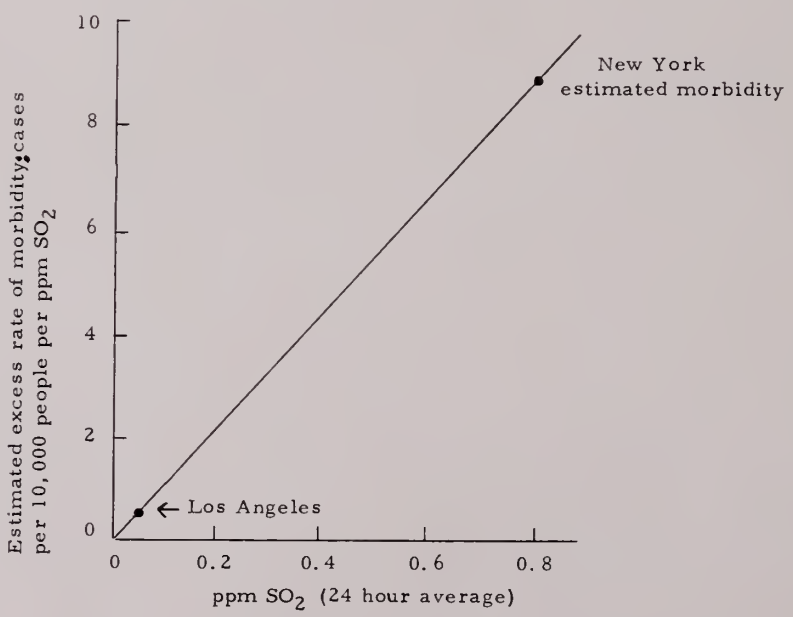
Sulfur dioxide was most consistently correlated for relevant disease. When the disease rate for various categories was analyzed for days of the low ⅓ of SO_2 concentration and for days of the high ⅓ SO_2 concentration, the categories of infectious disease, acute respiratory infection and bronchitis showed the greatest increase on high SO_2 days. The excess morbidity for these diseases on high SO_2 days would amount to 55 cases per 10,000 admissions. The authors point out that SO_2 is not considered a major pollutant in the Los Angeles area, and their own graphs indicate the highest daily average to be only 0.0135 part per million. If the morbidity effects were linear and if the SO_2 were as much as three times normal during high SO_2 days, this rate of excess admissions due to air pollution would be 1,000 per 10,000 admissions per parts per million SO_2 for highly relevant disease.

In a New York study[10] a variety of air pollution factors were measured along with the death rates on five occasions when temperature inversions occurred with sharp rises in SO_2 concentration. From this study of excess mortality, an estimate of air pollution death rates would give a minimal value of about 0.03 deaths per 10,000 people per parts per million SO_2 for a 24-hour period. This rate is based on excess deaths occurring on December 1, 1962, con-

sidering only the cases greater than two standard deviations from the mean. No other unusual diseases were present.

In the Donora, Pennsylvania, pollution episode in 1948, 20 people died and about 5,000 became ill.[11] The ratio of deaths to illness from this tragedy would be 1/300. If this ratio can be applied to New York, then the death rate, 0.03 per 10^4 people per parts per million SO_2, would be proportional to a morbidity rate of nine cases/10^4 people/parts per million. The Los Angeles area showing a rate of 1000/10^4 admissions/parts per million for low levels of SO_2 air pollution coupled with a total admission rate of 0.6 admissions per 10^4 people (calculated from a crude admission rate of 150 cases/2.5 x 10^6 people) would give a morbidity rate related to pollution of 0.06 cases/10^4 people/parts per million. This suggests a non-linear-dose response curve with great morbidity at higher SO_2 levels. However, the Los Angeles data may be ten-fold or more underestimated since it deals with hospitalized cases, while it is likely that a much larger group with symptoms would remain at home. If one assumes a 1:10 ratio of admissions to total cases, the Los Angeles rate of morbidity would be about 0.6 cases/10^4 people/parts per million. Interestingly enough, if one plots these rates for New York and Los Angeles, a line connecting these points passes through zero, suggesting a linear dependence of morbidity rate normalized per parts per million SO_2 vs. parts per million SO_2 level (Figure 1). The actual excess morbidity rate dependence on SO_2 would approximately obey the mathematical function $y = mx^2$ (y = excess morbidity rate, x = parts per million SO_2) (Figure 2).

Other facts from the New York study indicate that the lag time for possible acute pollution-related deaths may be as short as one day and that the SO_2 concentrations in these episodes ranged from 0.2 part per million to peaks during inversions of 0.8 part per million (24 hour averages.) Furthermore, in some cases, not just the aged were affected but also the middle-aged. From



Estimated excess morbidity rates for air pollution in high and low SO_2 cities.

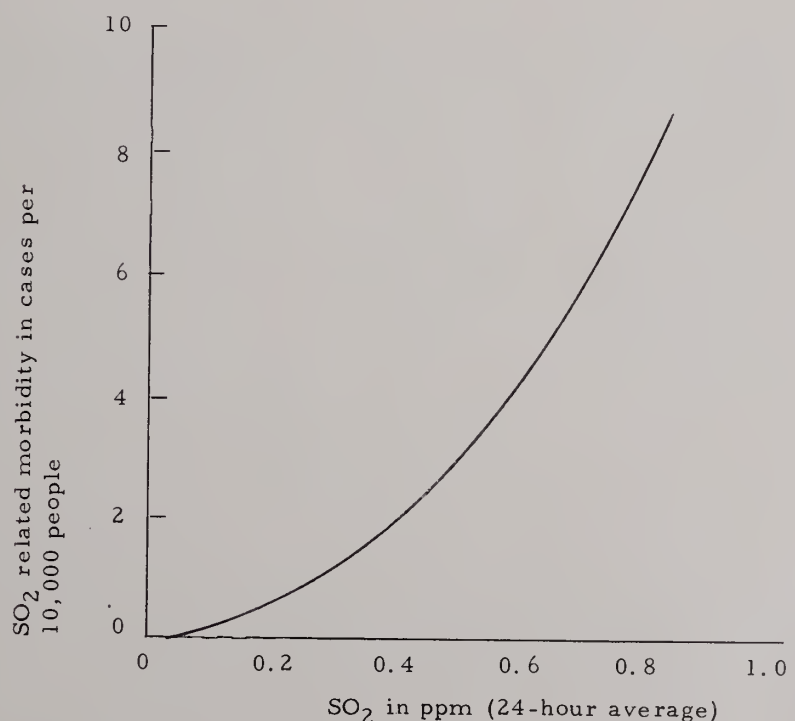
Figure 1

this evidence the threshold of excess death may be as low as 0.5 part per million for 24 hours.

Dr. Stephan Ayres points out that while guinea pigs are sensitive to 0.1-0.2 part per million SO_2, humans seem not to be sensitive until the level 5 parts per million SO_2 is reached.[12] This points out the present dilemma in dealing with pollution at a quantitative level. There seems to be a 15-fold discrepancy between effective acute laboratory concentrations and atmospheric levels of SO_2 which epidemiologically seems effective. It must, however, be emphasized that laboratory experiments in this case have neither resolved the problem of time-dose relationship between SO_2 and physiological injury nor the effect of any SO_2 concentrations on debilitated subjects. The latter cannot be done with human subjects for ethical reasons. Even if there were a 15-fold discrepancy between epidemiological effects and laboratory experiments with normal volunteers, one still might presume that the aged and debilitated in major cities might be 10 to 15-fold more sensitive to SO_2 and particulates. And if one were to develop standards geared to the most sensitive individual, which is what must be done, then the presently-proposed Minnesota state standards seem reasonable. These standards call for a maximum eight-hour concentration average of 0.1 part per million.

Smoking

Children have been ideal candidates for epidemiological studies since they generally do not smoke. The following facts have emerged: Peak respiratory flow rates are depressed in children living in heavily polluted industrial areas.[19,20,21] An important epidemiological study indicated that lower res-



Estimated excess morbidity rate for SO_2 containing city atmospheres.

Figure 2

piratory infections in children were related to air pollution, while upper respiratory diseases were not.[22] In another study upper respiratory disease, lower respiratory disease and depression of FVC and $FEV_{0.75}$ were related to air pollution.[23]

In terms of these details it is useful to examine Bates' preliminary synthesis of a variety of information on the natural history of chronic bronchitis and emphysema.[24] Cigarette smoking causes a primary effect on the small bronchioles leading to impaired defense against infection which is aggravated by areas of high industrial pollution. After some years of smoking, measurable effects of lung function will be observed, the time dependent on city or country dwelling. With continued exposure to smoking or pollutants, hypertrophy of mucous glands appears with increased sputum production and decrease of forced expiratory volume. Bronchioles begin to disappear and ventilation depends in some areas on collateral drift. Blood gases begin to be abnormal. In the next phase lung tissue starts to break down, with the occurrence of centrolobular emphysema. Finally with further damage comes panlobular emphysema.

Conclusion

There is substantial evidence that a large health cost must be attributed to air pollution. It appears to me that industrial consultants in Minnesota probably have underestimated the health hazards of fossil fuel combustion. It seems appropriate that the public should know the level of air pollution on a day-to-day basis in the Minneapolis and St. Paul metropolitan areas. As of now, pollution levels are not generally published even though they may be considerable. On a national scale studies need to be done to place the morbidity rate from air pollution in quantitative terms so that the relative population dangers can be assessed. A broader type of medical and scientific expertise needs to be brought to this problem at a state administrative level to safeguard the public health. Finally, we must at this point still be cautious in setting standards to accommodate industry, standards which at a later time may be found to be detrimental to human health.

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11-24. May be secured from the author.

Derivatively Speaking

Bunion—from Greek *bounion* (turnip).

Anesthesiology

Regional Anesthetic Blocks

In spite of the advances in anesthesiology there are still many times when a regional anesthetic, such as a block of an arm or a leg, is a much safer procedure than a general anesthetic. Most surgeons are aware of the hazards of general anesthesia in patients with full stomachs, impending shock, or respiratory disease. Yet not many modern surgeons have had an opportunity to become experienced with local blocks other than local infiltration anesthesia. Because many operations are still performed where anesthesiologists are in short supply and where the operating surgeon must somehow manage the anesthetic himself, we are presenting a series of reviews of the basic regional anesthetic techniques. These techniques have been chosen because they are easy to learn, simple to perform and most valuable to the practicing surgeon.

The reader is urged, nevertheless, to supplement this review with one of the texts listed in the bibliography.

The Wrist Block

The nerves to the hand can be blocked at several different points: at the brachial plexus as it crosses the clavicle, in the axilla, at the elbow and at the



Fig. 1—The median nerve is blocked at the wrist where it lies under the palmaris longus tendon.

wrist. The last approach will be reviewed here because it meets our criteria of ease in learning, simplicity in execution, and effectiveness.

Three nerves enter the hand at the wrist: the radial, the median and the ulnar nerves. The median and ulnar are deep and lie in compartments, so that to ensure their accurate location a paresthesia should be elicited with the needle point before one injects the drug. The radial nerve is superficial and divided and can therefore be blocked simply by infiltration as described below.

Eliciting a paresthesia should be done carefully to minimize discomfort to the patient. The operator should warn the patient that he will soon feel "a lightning like sensation" or "a tingling" in the distribution of the nerve. The patient should be instructed to say "Now" when he feels the paresthesia. Gaining the patient's cooperation is important for success and does not add unduly to his anxiety if one assumes a cool and reassuring manner.

Indications

A wrist block will produce anesthesia of the entire hand and is appropriate for any surgery which can be accomplished in 1½ hours. A tourniquet can be placed around the wrist after the block is performed and will be well tolerated if carefully applied. The skin of the wrist should be washed, treated with an antiseptic and draped with sterile towels.

Locate the Median Nerve

The median nerve lies just below the palmaris longus tendon. With the



Fig. 2—The ulnar nerve is blocked where it lies deep to the flexor carpi ulnaris tendon.

hand lying supine the patient is asked to press the tips of the thumb and little finger together while the wrist is flexed. This causes the palmaris longus tendon to stand out. A 25-gauge needle is inserted past the tendon to a depth of 1.0 cm. Gentle fan-wise probing with the needle will elicit a paresthesia into the palm of the hand. Five cc of anesthetic agent are then injected. If paresthesia recur during injection the needle should be moved slightly so that the drug is not deposited intra-neurally. The median nerve supplies the radial half of the palm and the palmar surface of the thumb and first two fingers plus the radial edge of the third finger.

Locate the Ulnar Nerve

The ulnar nerve lies directly under the tendon of the flexor carpi ulnaris: that tendon that lies in the ulnar-ventral corner of the wrist. It can be approached from either the ventral or the medial surface. A paresthesia should be elicited with a short 25-gauge needle to confirm accurate positioning of the needle; then 3 to 4 cc of anesthetic agent are injected, taking care not to inject into the nerve or the artery. This will produce anesthesia of the ulnar third of the hand, the fifth finger and half of the fourth finger.

Locate the Radial Nerve

The radial nerve lies superficial to the tendons and fascia of the wrist and can therefore be blocked by a subcutaneous band across the "snuff box" on the radial side of the wrist. About 6 or 8 cc are injected in a band around the radial side of the wrist over the extensor tendons to the thumb. The drug

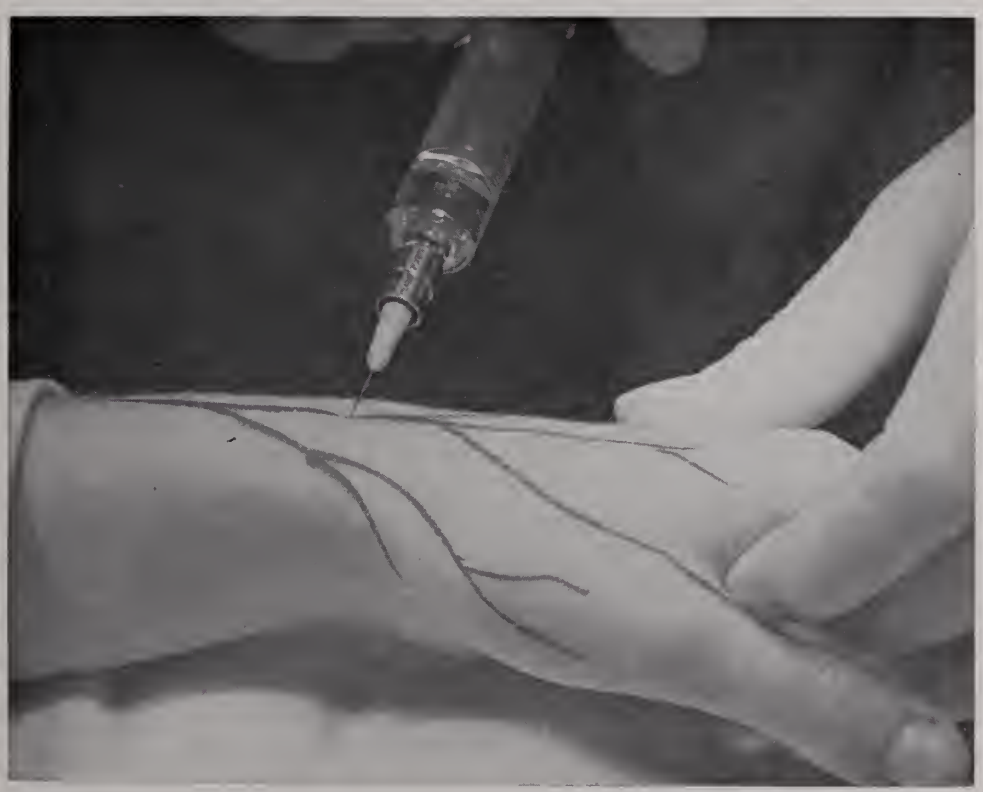


Fig. 3—The radial nerve is blocked at the wrist by injecting subcutaneously across the "snuff-box."

should be well distributed between skin and fascia so that a wall of drug is deposited through which all the fibers traverse.

The Anesthetic Agent

Epinephrine is not used, nor should it be added to the anesthetic agent, because of the danger of producing ischmia of the fingers. For that reason we recommend mepivicaine (Carbocaine) 1% as the agent of choice. However, lidocaine (Xylocaine) 1%, procaine 2% or tetracaine (Pontocaine) 0.15% would be satisfactory.

Be patient. It requires 15 to 20 minutes to take effect. Care should be taken that the nerves are not traumatized by the needle or drug. Paresthesia should be elicited gently to minimize discomfort.

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Special Article

Vietnam Malaria

Clinical Experience with 50 Patients

THE CONFLICT IN Vietnam has resulted in the admission of 50 patients for treatment of malaria at the Minneapolis Veterans Administration Hospital. Of these 50 patients, 40 had vivax* and nine had falciparum malaria.* The single remaining patient suffered from a mixed infection with both species of plasmodia. In this study, our clinical and therapeutic experiences with these patients are presented.

Material and Methods

The cases selected for the study included all of the Vietnam malaria patients admitted to our hospital in the last three years. The diagnosis was confirmed in every case by demonstration of malarial parasites in thick and thin smears of peripheral capillary blood. Blood smears were examined repeatedly during the course and at the conclusion of antimalarial therapy.

All patients with vivax infections received a course of chloroquine and primaquine initiated at the same time. One gram of chloroquine phosphate was given on the first day and 0.5 gm. daily for the next three days. Primaquine was given in a daily dose of 15 mg. (base) for two weeks. In case of a relapse a similar course of chloroquine-primaquine was repeated.

In 1966 three patients with falciparum malaria were given a course of chloroquine to test the possibility of chloroquine-resistance. All these patients failed to respond to this form of therapy and it was consequently abandoned. Four patients with falciparum malaria (including the three chloroquine failures) received quinine and primaquine therapy. Quinine sulfate was given orally in doses of 0.65 gm. every eight hours for a period of two weeks; primaquine was administered in the same dose schedule as in patients with vivax malaria. In the subsequent six patients with falciparum malaria, sulfadiazine and pyrimethamine were given for a five-day period along with quinine sulfate; the dose of sulfadiazine was 0.5 gm. four times daily and that of pyrimethamine 50 mg. once daily.

A majority of the patients with a relapse of malaria were re-admitted and followed in our hospital. A questionnaire was sent to all patients regarding further attacks of malaria. Records of admissions to other hospitals were also obtained.

Findings

Source of Infection

All patients were white males of the average age of 22 years. Average duration of stay in Vietnam had been eight months. Thirty-eight patients had been stationed in the central highlands of Vietnam and 12 had served in other areas of Vietnam.

Prophylaxis

In Vietnam, all patients had taken the once weekly chemoprophylaxis of chloroquine (300 mg. of base) and primaquine (45 mg. of the base); some were also given a daily prophylaxis (diphenyldiaminosulfone, 25 mg.). Despite this, 21 patients had suffered attacks of malaria while in Vietnam. In 16, these attacks were caused by *Plasmodium falciparum* and in five by *P. vivax*.

Patients with falciparum infections became ill soon (one to nine weeks, mean three weeks) after their return from Vietnam, whereas vivax infections generally appeared later (one to 44 weeks, mean 11 weeks). The veterans were supposed to take the chloroquine-primaquine prophylaxis for a period of eight weeks after their return to the U.S.A., but they admitted

*See Test Your Word Score, Page 277.

taking the prophylaxis for a mean period of only four weeks (range one to eight weeks).

Clinical Manifestations

The clinical findings are summarized in Table 1. Except for spontaneous rupture of spleen in one patient and probable cerebral involvement in another, we have not observed complications of falciparum malaria, such as blackwater fever, renal failure, nephrotic syndrome or pulmonary involvement.

Laboratory Observations

Selected laboratory findings are summarized in Table 2. Anemia, when present, was normocytic and normochromic in nature. The white blood cell count was normal in the majority of patients, but 36% had leukopenia during the illness. Leukocytosis was not observed.

Thirty patients had quantitative platelet counts and 80% had thrombocytopenia. In the patients without quantitative counts, the peripheral blood smear showed decreased platelets. Five patients with positive serology for syphilis (VDRL) were negative when tested with the fluorescent treponema antibody test. Direct and indirect Coomb's tests were negative in three patients with falciparum malaria.

TABLE 1
Clinical Findings

Symptoms	No.	Percent
Fever & chills	50	100
Headache	33	66
Nausea & vomiting	27	64
Muscle pain	20	40
Abdominal cramps & diarrhea	8	16
Signs		
Palpable spleen	44	88
Palpable liver	22	44
Icterus	4	8

TABLE 2
Laboratory Findings

Abnormality	No-of Pts. Tested	Pts. Showing Abn. Findings, %	Range
Anemia	50	46	5.8-12 gm/100 ml
Leukopenia	50	36	3,000-4,700
Thrombocytopenia	30	80	12,000-150,000
Reticulocytosis	36	42	3-18%
VDRL	30	16	
Liver Function Tests			
Serum bilirubin	47	46	1-1.8 mg/100 ml
SGOT	40	10	40-108 units
Alk. p'tase	35	17	11-27 units
Ceph. floc.	25	76	3+-4+
Feces—ova & parasites	40		
Ancylostoma duodenale		20	

Complications

Except for two patients with complicated falciparum infections, one with a ruptured spleen and one with mixed infection, the patients with falciparum malaria did not show more severe laboratory abnormalities than the patients with vivax malaria.

Results of Therapy

The results of therapy and the relapse rate are summarized in Table 3. All patients with vivax malaria responded to a single course of chloroquine-primaquine with prompt symptomatic recovery and negative blood smears within 48 hours. There were no complications in these patients.

Twenty-eight patients with vivax malaria were followed for an average of 30 weeks. Five had a recurrence of their illness, all within 20 weeks. One patient suffered a total of four attacks. Retreatment with chloroquine and primaquine resulted in prompt recovery without complications.

All 10 patients with falciparum malaria (including one with mixed infection and three chloroquine failures) responded to quinine in combination with other drugs (Table 3). One patient became asymptomatic on quinine therapy but his smears remained positive for 10 days.

Six patients with falciparum malaria were followed for a mean period of 58 weeks (Table 3). Two treated with quinine-primaquine had a relapse of their illness within four weeks of the initial attack. None of the remaining four patients treated with quinine, pyrimethamine and sulfadiazine suffered during followup from a relapse due to falciparum infection.

Comments

A very high percentage of U.S. troops in the central highlands of Vietnam have developed malaria; *P. falciparum* caused approximately 90 per cent of the infections.[1,2] In contrast to this, *P. vivax* has been responsible for 80% of infections becoming apparent after return to the U.S.A.[1,3] We have had a similar experience among our patients. From these observations, it appears that chloroquine-primaquine chemoprophylaxis, used in Vietnam, suppresses vivax infection adequately but *P. falciparum* breaks through this prophylaxis because of its resistance to chloroquine. When this chemoprophylaxis is discontinued, as occurs in the U.S.A., then vivax malaria is more likely to be manifest, on account of its secondary exoerythrocytic cycle in the liver.

Variable Clinical Symptoms

The clinical signs and symptoms of malaria may vary greatly. The disease should be considered in every febrile patient who has returned from Vietnam or other nearby areas of southeast Asia. Chills, followed by fever and sweating, constitute the characteristic malaria paroxysm. The classic pattern in both vivax and falciparum malaria is fever on alternate days; however, because of asynchrony in the development of parasites in the blood, a continuous or remittent fever may occur, as we have seen in some patients. A few may show parasitemia without any symptoms.

Hematologic Abnormalities

Many interesting new hematological abnormalities have been recently observed in malarial patients. Thrombocytopenia was commonly observed among our patients during the acute phase, and it has also been shown to occur in experimentally-induced human vivax malaria.[4] Depletion of other coagulation factors in drug-resistant falciparum malaria has also been reported.[5] Some degree of hemolytic anemia is usually present in patients with malaria, as evidenced by an increase in indirect-reacting serum bilirubin, erythroid hyperplasia of bone marrow and reticulocytosis. Thrombocytopenia, leukopenia and hemolytic anemia, as often seen in malaria patients, could be explained on the basis of hypersplenism. Coomb's positive immune hemolytic anemia has also been described in malaria patients,[6] yet in three of our patients with falciparum malaria and anemia the Coombs' test was negative. It has been recently postulated that hemolysis in malaria is due to the loss of negative charge from the surface of red blood cells (premature aging), which causes sludging and agglutination of these cells, resulting in their premature destruction in the circulating blood and reticuloendothelial system.[7]

Treatment

Treatment of vivax malaria has remained simple, and serious complications have rarely been observed. A course of chloroquine-primaquine is sufficient to treat an acute attack. A few patients with vivax malaria will suffer from a relapse within two years of their primary infection, and a course of chloroquine-primaquine should be repeated in such patients.

Treatment of falciparum malaria is still under evaluation and subject to change. In patients in Southeast Asia, chloroquine has

TABLE 3
Results of Therapy and Relapse Rate

Therapy	Total No. Treated*	Failures	Total No. Followed†	No. with Relapses
P. vivax	41		28	5
Chloroquine & Primaquine		0		
P. falciparum				
Quinine & Primaquine	4	0	2	2
Quinine, Pyrimethamine & Sulfadiazine	6	0	4	0

*Total no. is 51 due to one patient having mixed infection.
†Average follow-up: *P. vivax* 30 weeks
P. falciparum 58 weeks

been proven ineffective for the treatment of falciparum malaria. Quinine therapy is more reliable in treating these patients but, when used alone, 70-90% of the patients have suffered relapses of their infection.[2] Combined drug therapy has proved more effective. Among the various recommended drug combinations for the treatment of falciparum malaria, therapy includes: Quinine sulfate 0.65 gm. three times daily for two weeks, pyrimethamine 50 mg. per day for five days and sulfadiazine 0.5 gm. four times daily for five days. All three drugs should be started simultaneously. With combined drug therapy the relapse rate among falciparum malaria patients has dropped to 5%.[1,2] If a recrudescence does occur, the treatment should be repeated.

The incidence of potentially lethal complications among falciparum malaria patients has been low. Complications such as acute renal failure, cerebral malaria, blackwater fever and pulmonary involvement were seen elsewhere in only 1.1% of 3,300 falciparum cases and resulted in a total fatality rate of only 0.3%.[8] Prophylactic therapy, resulting in a low degree of parasitemia, seems the most likely explanation for this low incidence of complications. Early detection and vigorous therapy have also helped to lower the mortality rate.

Conclusions

Forty patients with vivax malaria, nine patients with falciparum malaria and one patient with mixed infection were seen in a three-year period at the Minneapolis Veterans Administration Hospital. The clinical findings, laboratory studies, therapy and results are presented.

Acknowledgment

We wish to acknowledge the assistance given by Arthur Sanders, B.A., and Franklin Wallace, Ph.D., in the parasitologic diagnosis of these patients.

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Motivation

There are many highly respectable motives which may lead men to prosecute research, but three which are much more important than the rest. The first (without which the rest must come to nothing) is *intellectual curiosity*, desire to know the truth. Then, *professional pride*, anxiety to be satisfied with one's performance, the shame that overcomes any self-respecting craftsman when his work is unworthy of his talent. Finally, *ambition*, desire for reputation, and the position, even the power or the money which it brings. It may be fine to feel, when you have done your work, that you have added to the happiness or alleviated the sufferings of others, but that will not be why you did it. So if a mathematician, or a chemist, or even a physiologist, were to tell me that the driving force in his work had been the desire to benefit humanity then I should not believe him (nor should I think the better of him if I did). His dominant motives have been those which I have stated, and in which, surely, there is nothing of which any decent man need be ashamed.*

**Motivation*, by G. H. Hardy, from "A Mathematician's Apology," Cambridge at the University Press, 1967.

Meetings and Announcements

Conference on Rural Health

23rd National Conference on Rural Health, April 9-10, 1970, Pfister Hotel and Tower, Milwaukee, Wisconsin. Contact: Council on Rural Health, American Medical Association, 535 North Dearborn Street, Chicago, Illinois 60610.

Drug Abuse Symposium

"Spiritual and Medical Resources for the Drug Scene," to be held at Lutheran Brotherhood Insurance Company Auditorium, 701 2nd Avenue South, Minneapolis, all day on Saturday, April 18, 1970.

The Symposium is approved for six and a half prescribed credits in continuation study by the Minnesota Academy of General Practice. Registration fee is $5.00 including luncheon. Application can be made to Miss Hulda Buegel, R.N., 6025 Goodrich Ave., Minneapolis, Minnesota 55416.

New Jersey Medical Society Meeting

The Medical Society of New Jersey 204th Annual Meeting, Saturday-Tuesday, May 16-19, 1970, Haddon Hall, Atlantic City. Contact: The Medical Society of New Jersey, 315 West State Street, Trenton, N. J. 08618.

April Meetings

Spring Refresher, Wednesday-Thursday, April 1-2, Annual Meeting, Minnesota Academy of General Practice, Hotel Radisson, Minneapolis, Minnesota.

Head & Neck, Sunday-Tuesday, April 12-14, Society of Head and Neck Surgeons, Mayo Clinic, Rochester, Minnesota.

Occupational Medicine, Thursday, April 16, Minnesota Academy of Occupational Medicine and Surgery, Minneapolis Club, 729 Second Avenue South, Minneapolis, Minnesota. Program Chairman: Edwin G. Benjamin, M.D.

Continuation in Trauma, Friday, April 17, Nolte Center, University of Minnesota. Chairman: Dr. James House, "Trauma and Diseases of the Upper Extremities", Fee: $30.00. Limit: 80. AMA Credit: seven hours.

May Day Meeting, Saturday, April 18, "Infectious Diseases", Duluth Clinic, Ltd., Duluth, Minnesota. Location: London House, 2502 London Road, Duluth, Time: 10:00 a.m. to 5:00 p.m. Guest Speaker: Dr. Maxwell Finland, Minot, Professor of Medicine, emeritus, Harvard Medical School, Boston, Mass.

The Dreadful Adventure of the Windmills*

"As they discoursed, they discovered some thirty or forty windmills, that are in that field; and as soon as Don Quixote espied them, he said to his squire, 'Fortune doth address our affairs better than we ourselves could desire; for behold there, friend Sancho Panza, how there appears thirty or forty monstrous giants, with whom I mean to fight, and deprive them all of their lives, with whose spoils we will begin to be rich; for this is a good war, and a great service unto God, to take away so bad a seed from the face of the earth.'

" 'What giants?' quoth Sancho Panza.

" 'Those that thou seest there,' quoth his Lord, 'with the long arms; and some there are of that race whose arms are almost two leagues long.'

" 'I pray you understand,' quoth Sancho Panza, 'that those which appear there are no giants, but windmills; and that which seems in them to be arms, are their sails, that, swung about by the wind, do also make the mill go.'

" 'It seems well,' quoth Don Quixote, 'that thou are not yet acquainted with matter of adventures. They are giants; and, if thou beest afraid, go aside and pray, whilst I enter into cruel and unequal battle with them.' And, saying so, he spurred his horse Rosinante without taking heed to his squire Sancho's cries, advertising him how they were doubtless windmills that he did assault, and no giants; but he went so fully persuaded that they were giants as he neither heard his squire's outcries, nor did discern what they were, although he drew very near to them, but rather said, as loud as he could, 'Fly not, ye cowards and vile creatures! for it is only one knight that assaults you.'

"With this the wind increased, and the mill sails began to turn about; which Don Quixote espying, said, 'Although thou movest more arms than the giant Briareus thou shalt stoop to me.' And, after saying this, and commending himself most devoutly to his Lady Dulcinea, desiring her to succor him in that trance, covering himself well with his buckler, and setting his lance on his rest, he spurred on Rozinante, and encountered with the first mill that was before him, and, striking his lance into the sail, the wind swung it about with such fury, that it broke his lance into shivers, carrying him and his horse after it, and finally tumbled him a good way off from it on the field in evil plight. Sancho Panza repaired presently to succor him as fast as his ass could drive; and when he arrived he found him not able to stir, he had gotten such a crush with Rozinante.

" 'Good God!' quoth Sancho, 'did I not foretell unto you that you should look well what you did, for they were none other than windmills? nor could any think otherwise, unless he had also windmills in his brains.'

" 'Peace, Sancho,' quoth Don Quixote."†

*See page 279.

†Don Quixote of the Mancha-Miguel de Cervantes—Harvard Classics.

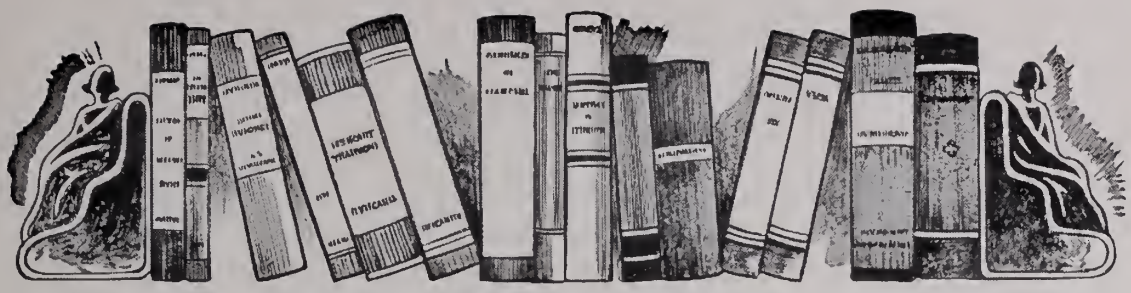
Secret study, silent thought, is, after all, the mightiest agent in human affairs.
—Channing.

An optimist notes the green lights. A pessimist sees the red. A philosopher is color-blind.—M. Dale Baughman: Treasury of Stories.

Annual Meeting

Minnesota State Medical Association

The annual meeting this year will be held in Duluth, May 18 through May 20, at the Civic Auditorium and the Duluth Hotel. Official programs and pre-registration material will be mailed before the meeting.



Book Reviews

The proper study of mankind is books.—Aldous Huxley

HAND BOOK OF OCULAR THERAPEUTICS AND PHARMACOLOGY—Third Edition; Authors: Ellis and Smith, C. V. Mosby Company; Price: $10.75.

Dr. Philip P. Ellis, an ophthalmologist, and Dr. Donn L. Smith, a pharmacologist, have combined their expertise and their individual disciplines to produce a most useful book. This handbook is divided into two sections, the first called Ocular Therapeutics, in which both general principles of treatment and details of treatment of specific ocular disease are considered. The second section entitled, Pharmacology—Therapeutic Agents, deals with specific medications commonly utilized in the treatment of ophthalmic disease. The specific drugs are listed in alphabetic order and comments are made pertinent to their actions, ophthalmic uses, side reactions, contraindications, preparations and dosage.

The present book is the third edition, the second having been printed in 1966. As noted in the preface to this current edition, new therapeutic agents including various antibiotics and anti-inflammatory drugs, autonomic nervous system agents and antiglaucoma medications have been added. This edition also reports newly reported side reactions to local and systemic ocular medications. Pediatric dosage tables have been expanded.

This handbook is hard bound, contains 251 pages inclusive of index, and is published by the C. V. Mosby Company. In addition to good general organization of the book so that individual items of interest may be found, there are several good summary tables and a good general index.

This is not the type of book which would be ordinarily read from cover to cover, but is an excellent reference source containing much information easily available pertinent to the clinical problems which arise in the area of eye therapeutics and pharmacology. I highly recommend it as a reference text for all individuals involved in eye therapeutics and pharmacology. It will particularly appeal to and be useful to the clinician.

Irving Shapiro, M.D.
Minneapolis, Minnesota

MEDICAL INTERVIEWING. Authors: Froelich and Bishop; Publisher: The C. V. Mosby Company; Price $4.75; Pages: 116.

This is a manual composed of questions and answers designed to improve the method of an adequate interview with the patient.

Surely the history of any illness and the manner in which the physician deals with his patient are important in every illness.

Without doubt, this would be of interest to the young doctor who is desirous of learning the gracious approach to a patient and his problems. To the seasoned physician who may have become a bit callous and cynical it is a good reminder that he should be more gentle and understanding; but to the physician who has gained an enviable reputation, because of his genuine compassion and interest in the individual, it would have scarcely any value. Unfortunately, of that type of a physician among us, there are all too few, in this day of hustle and hurry.

Carl O. Rice, M.D.
Minneapolis, Minnesota

ADRENERGIC NEUROTRANSMISSION; Edited by G. E. W. Wolstenholme and Maeve O'Connor; Ciba Foundation Study Group No. 33; (1968) Little Brown and Company, Boston; 123 pages, 12 illustrations.

Seven distinguished scientists from among the 22 participants attending the 1968 Ciba study group on adrenergic neurotransmission present selected papers which crystallize advances in this important area of biochemical research since the 1960 symposium.

The monograph serves as a ready source book for both historical and timely references on anatomical, biochemical and physiological aspects of non-adrenalin synthesis, localization, storage and release mechanisms. Its value to the interested reader is heightened by the enlightened discussions of the participants. The "Closing Discussion" is in itself worthy of close attention, as Professor Von Euler, in whose honor the meeting was held, consolidates many important relationships developed or alluded to in the preceding presentations.

The work should be of interest to scientists working in this area as well as to the advanced student desirous of acquiring additional knowledge of relatively current work and important references in adrenergic neurotransmission. Unlike some Ciba monographs, it will be of limited value to clinicians or persons working in the field of behavior disorders.

John J. McCutchen, M.D.
Houston, Texas

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AVAILABLE: Well established General Practice for one or two physicians. Present physician is returning to graduate school. New, well equipped clinic located in a prosperous, progressive community of 1200, 28 miles from Downtown Minneapolis. Four hospitals in immediate vicinity. Any terms available. Contact R. E. Simms, Security State Bank of St. Michael, St. Michael, Minnesota. Telephone 612-673-2131.

DEPARTMENT CHIEF and General Practitioners for Medical-Surgical Department of 1900 bed JCAH approved Mental Hospital. Salary to $29,000 depending on training and experience. Excellent fringe benefits. College town. Summer-winter sports area. Near Interlachen National Music Camp. Small town peace and quiet—big city culture. Contact M. Duane Sommerness, M.D., Supcrintendent, Traverse City State Hospital, Traverse City, Michigan 49684. An equal opportunity employer.

WANTED: General Practitioner, Internist, Pediatrician, Orthopedic Surgeon for the Bemidji Clinic of Bemidji, Minnesota. Outdoor sports advantage second to none. The Bemidji Clinic now consists of four general practitioners, one internist, two general surgeons, one obstetrician, and one ophthalmologist. If interested contact Duane E. Carlson, Business Manager, Bemidji Clinic, Bemidji, Minnesota.

EXCEPTIONAL OPPORTUNITY (full time position) as Assistant Medical Director in Home Office of Northwestern National Life Insurance Co., Minneapolis, Minn. Preferably General Practitioner or Internist. Minimum experience required: 2 or 3 years' practice or residency. Five-day week with full fringe benefits including group life, hospitalization, major medical, disability income, non-contributory retirement plan and paid vacations. Salary open. Send curriculum vitae in first letter to Dr. John G. Walsh, Medical Director, NWNL, Box 20, Minneapolis Minn. 55440 or call 612-372-5446.

EDUCATION PLUS: What midwestern high school of 170 boys currently has alumni at Harvard, Princeton, Swarthmore, M.I.T., McGill, London and Oxford (Rhodes Scholar), welcomes Americans, and produces great hockey teams? St. Johns-Ravenscourt School, Winnipeg 19, Manitoba. Headmaster: H. John P. Schaffter, M.A. (Cambridge), 204-453-3016.

WANTED: General practitioner to join two young general practitioners in well-established practice in suburban St. Paul. Excellent office space with lab, x-ray, and emergency room. Salary negotiable, with an association leading to early partnership opportunity. Write MINNESOTA MEDICINE 412, 375 Jackson St., St. Paul 55101.

GENERAL PRACTITIONER wanted to join well-established practitioner. New clinic building—90 miles east of St. Paul—city of 14,000. Early partnership with full hospital facilities. Ideal location. L. W. Picotte, M.D., Chippewa Falls, Wisconsin.

ST. PAUL—Spacious medical suite in new split-level building, part of a one block medical-dental complex adjacent to large shopping center. 1504 White Bear Avenue, 774-7144.

NEW EXPANDING OPPORTUNITIES for family physicians and physicians specializing in pediatrics, general surgery, internal medicine, urology, radiology, anaesthesiology; in medically-awakening community. Contemporary, automated, 105-bed, new hospital to be completed in the fall of 1970. Present hospital to be converted into long-term unit. Patient service area 50,000 people. Medical staff leading and supporting recruitment efforts. Excellent community location, forty miles equidistant to Milwaukee or Madison. Complete educational, cultural and recreational facilities. Possibility of new medical office building adjacent to new hospital. Immediate satisfaction in practice, income and family living. Special assistance if needed. Write or call Leo C. Bargielski, Administrator, Watertown Memorial Hospital, 1301 E. Main Street, Watertown, Wisconsin, 53094; telephone 414-261-4210 for more information.

GP AND OB GYN wanted to join two GPs, surgeon, and internist in suburban group. Excellent nearby hospital. Salary first year, then partnership. Write MINNESOTA MEDICINE-436, 375 Jackson, St. Paul 55101.

EXCELLENT OPPORTUNITY for General Practitioner and General Surgeon to join 4-man general practice group. Services of Radiologist immediately available. Liberal time off and post graduate allowances. Salary open with opportunity for early partnership. College town, population of 10,000, 30 miles from Minneapolis-St. Paul. Edward A. Jenkins, Manager, River Falls Medical Clinic, River Falls, Wisconsin 54022. Phone number 425-5322.

GENERALIST — INTERNIST — OPHTHALMOLOGIST NEEDED IN FAIRMONT, MINNESOTA. Will begin construction of a new 115 bed hospital and a large medical clinic next spring. Lovely community of 13,000 population centered around a chain of lakes in Southern Minnesota. Excellent public schools with a new junior college scheduled to open in 1973. Two doctors' offices presently have space for another man. Call or write Robert Zemke, Generalist, Neil Nickerson, Internist or Cale Neal, Hospital Administrator.

INTERNIST AND GENERAL PRACTITIONER wanted to join a five-man clinic group in Minneapolis. Complete laboratory and X-ray with board roentgenologist. Excellent hospital staff associations. Salary arrangement to start with, early partnership. Write MINNESOTA MEDICINE—289; 375 Jackson, St. Paul, 55101.

Classified Advertisements

IMMEDIATE OPENING: Internist or General Practitioner to join six man multispecialty group in northeastern Wisconsin. Excellent professional opportunity to practice in a friendly community, only two actively practicing physicians (General Practitioners) in the community outside of our clinic. Salary commensurate with training and experience first year and then full partnership. Ideal, safe small city living for the family on scenic Lake Michigan with excellent fishing, boating and hunting. All this and still only 1½ hours drive to Milwaukee or 45 minutes to Green Bay or lovely Door County. For complete details contact Robert E. Myers, M.D., Garfield at 23rd, Two Rivers, Wisconsin 54241.

WANTED: Young physician for association leading to partnership with four well established General Practitioners in fast growing suburb of St. Paul. Excellent clinic facilities in nearly new, partnership owned, well equipped, medical center building. Write: MINNESOTA MEDICINE-421, 375 Jackson, St. Paul 55101.

PHYSICIAN WANTED: G.P.—join young group of 4 GP's 4 day office week, high earnings, early partnership, immediate work load. Well equipped, newer clinic, fully accredited hospital, excellent practice conditions. Call collect 612-445-1305. Shakopee Medical Center. J. E. Ponterio, M.D., Shakopee, Minn.

TEN MAN MULTISPECIALTY group needs an orthopedist, ophthalmologist and another pediatrician. New clinic building, complete laboratory and x-ray facilities. 180 bed modern hospital across street from clinic. Early share-holder status. Salary open. Write or call the Lenont-Peterson Clinic, Ltd., C. A. Tietz, M.D., area code 218, 741-4292, Virginia, Minnesota 55792.

THREE MAN group in North West Wisconsin Resort, State Conservation and Retirement Area needs two more physicians adequately to serve their practice. Facilities offered are three-room physician suites, X-ray and lab under AMT technician, RN-only nursing personnel. New accredited thirty-two bed hospital and forty-six bed nursing home. Deer and duck hunting, fishing within five minutes of town. Internist most needed; generalists welcomed. Will meet any reasonable salary request. Partnership after one year. Write: MINNESOTA MEDICINE—365; 375 Jackson St., St. Paul 55101.

PSYCHIATRIC RESIDENCIES: We offer nothing but excellent psychiatric training in a stimulating, well-organized program located in a culturally advantaged community. Approved psychiatric training. Traverse City State Hospital, Michigan Department of Mental Health. Three and five year programs. Salary, 3 year program: $10,669; $11,191; $12,131. 5 year program: $12,152; $14,031; $16,328; $21,944; $23,093. NIMH-GP stipends available. Located in Michigan's serene, scenic recreation area on Grand Traverse Bay. Contact Dr. Paul E. Kauffman, Director of Training, Traverse City State Hospital, Traverse City, Michigan 49684. An equal opportunity employer.

WANTED: Generalist to join well-established general practitioner. Fully accredited 125 bed hospital—120 miles north of Minneapolis in a superb recreational area—excellent fishing, hunting, etc., many churches, new schools. Salary negotiable. Write MINNESOTA MEDICINE—446, 375 Jackson Street, St. Paul, Minn. 55101.

WANTED: General Practitioner or Internist, to join four man group in St. Paul. Partnership possible in one year. Dr. V. L. Sommerdorf, 1239 Payne Avenue, St. Paul, Minnesota 55101.

Throw Back

One of my male students at Northwestern University was 22 years old. He dated a pretty coed who didn't know he had come over from Sweden at the age of 12, for he spoke perfect English and seemed unwilling to have anybody know of his foreign background. But at parties where liquor was served, if he had taken four or five drinks, he would soon begin to speak exclusively in Swedish and never utter a word in English. Why? Because the alcohol had dropped his mental age back to the 12-year mark which was when he left Sweden! At that age, he spoke only Swedish!*

*Dr. George Crane: The Quotable Dr. Crane, 1968.

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IMPORTANT NOTE: INDOCIN (Indomethacin, MSD) cannot be considered a simple analgesic and should not be used in conditions other than those recommended under Indications. The drug should not be prescribed for children because safe conditions for use have not been established.

General Adverse Effects: Because of the high potency of the drug and the variability of its potential to cause adverse reactions, the following are strongly recommended: 1) the lowest possible effective dose for the individual patient should be prescribed. Increased dosage tends to increase adverse effects, particularly in doses over 150-200 mg/day, without corresponding clinical benefits; and 2) careful instructions to, and observations of, the individual patients are essential to the prevention of serious and irreversible, including fatal, adverse reactions, especially in the aging patient.

Indications: Symptomatic relief of adult rheumatoid and degenerative joint disease unresponsive to adequate trial of salicylates and other measures of established value, such as appropriate rest. Has been found effective in active stages of: 1) moderate to severe rheumatoid arthritis including acute flares of chronic disease, 2) moderate to severe rheumatoid (ankylosing) spondylitis, and 3) moderate to severe degenerative joint disease of the hip (osteoarthritis of the hip). Has been found effective in relieving pain and reducing fever, swelling, and tenderness in acute gouty arthritis in selected patients. May enable reduction of steroid dosage in patients receiving steroids for the more severe forms of rheumatoid arthritis; in such instances the steroid dosage should be reduced slowly and the patients followed very closely for any possible adverse effects.

Contraindications: Children 14 years of age and under; pregnant women and nursing mothers; active gastrointestinal lesions or history of recurrent gastrointestinal lesions; allergy to aspirin and indomethacin.

Warnings: *Gastrointestinal Effects:* Because of the occurrence and, at times, severity of gastrointestinal reactions, be continuously alert for any sign or symptom signaling a possible gastrointestinal reaction. The risks of continuing therapy with INDOCIN in the face of such symptoms must be weighed against the possible benefits to the individual patient. Gastrointestinal effects may be reduced by giving the drug immediately after meals, with food, or with antacids. Use greater care in aging patients.
Ocular Effects: Corneal deposits and retinal disturbances, including those of the macula, have been observed in some patients on prolonged therapy. Discontinue therapy if such changes are observed. Ophthalmologic examination at periodic intervals is desirable in patients on prolonged therapy.
Central Nervous System Effects: INDOCIN (Indomethacin, MSD) may aggravate psychiatric disturbances, epilepsy, and parkinsonism, and should be used with considerable caution in patients with these conditions. If severe CNS reactions develop, discontinue the drug.

Precautions: Blurred vision may be a significant symptom that warrants a thorough ophthalmologic examination. Patients should be cautioned about engaging in activities requiring mental alertness and motor coordination, as driving a car. Headache which persists despite dosage reduction requires complete cessation of the drug. May mask the usual signs and symptoms of infection; therefore, the physician must be continually on the alert for this and should use the drug with extra care in the presence of existing controlled infection. After the acute phase of the disease is under control, an attempt to reduce the daily dose should be made repeatedly until the patient is off entirely.

Adverse Reactions: *Gastrointestinal Reactions:* Single or multiple ulcerations of the esophagus, stomach, duodenum, or small intestine, including perforation and hemorrhage, with fatalities in some instances; gastrointestinal bleeding without obvious ulcer formation; perforation of preexisting sigmoid lesions (diverticulum, carcinoma, etc.); rarely, increased abdominal pain in ulcerative colitis patients or development of ulcerative colitis and regional ileitis; gastritis, which may persist after the cessation of the drug; nausea, vomiting, anorexia, epigastric distress, abdominal pain, and diarrhea.
Eye Reactions: Corneal deposits and retinal disturbances, including those of the macula, have been observed on prolonged therapy; blurring of vision.
Hepatic Reactions: Rarely, toxic hepatitis and jaundice, including some fatal cases.
Hematologic Reactions: Aplastic anemia, hemolytic anemia, bone marrow depression, agranulocytosis, leukopenia, and thrombocytopenic purpura. Since some patients manifest anemia secondary to obvious or occult gastrointestinal bleeding, appropriate blood determinations are recommended.
Hypersensitivity Reactions: Acute respiratory distress, including dyspnea and asthma; angiitis; pruritus; urticaria; angioedema; skin rashes.
Ear Reactions: Hearing disturbances, deafness, tinnitus.
Central Nervous System Reactions: Psychotic episodes, depersonalization, depression, coma, convulsions, peripheral neuropathy, drowsiness, mental confusion, lightheadedness, dizziness, headache.
Cardiovascular-Renal Reactions: Edema, elevation of blood pressure, hematuria.
Dermatologic Reactions: Loss of hair, erythema nodosum.
Miscellaneous: Rarely, vaginal bleeding, hyperglycemia, glycosuria, ulcerative stomatitis, and epistaxis.

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Minnesota Medicine at a Glance

Treatment of Myelomeningocele—*Bunch and Geist* Page 245

For the doctor in private practice who occasionally sees the distressing congenital myelomeningocele, it is comforting to know that the prognosis need no longer be as grave as formerly. With the combined effort of the general practitioner and the properly indicated specialists these patients can be expected to attain a reasonably active life.

Retroperitoneal Fibrosis—*Larson and Doan* Page 251

Retroperitoneal fibrosis most often produces obstruction of the ureter, and presents symptoms of an obstructive uropathy. Rarely, obstruction of the retroperitoneal major vessels also occurs, with corresponding symptoms. The case reviewed revealed a totally obstructed vena cava as well as the iliac vein, and right ureter. Surgical decompression of the vena cava was not possible because the fibrosis had obliterated normal anatomical planes, but ureteral decompression was accomplished. The authors recommend earlier diagnosis in hope of facilitating surgical treatment.

Intra-Aortic Balloon Pumping—*Moulopoulos et al.* Page 261

In recent years, support of the failing heart has been attempted by various means. One of these means is intermittent inflation of a balloon placed within the thoracic aortic lumen. This paper details an experimental study on sheep wherein this mechanism proved helpful. The shortcomings and drawbacks of the procedure are clearly outlined. This is one of the least traumatic and best tolerated mechanisms of temporary left ventricular assist.

Medical Witness

"Lawyers frequently refer to medical witnesses as adverse, impartial, advocate or independent. These generally have a specific meaning for lawyers. While physicians normally attempt to give an honest, straightforward medical opinion, lawyers normally regard a medical witness as an *advocate* for the person on whose behalf he is testifying in court. In other words, if a physician testifies for either the plaintiff or the defendant, he is regarded as an advocate for the claim of the person for whom he is testifying. If a physician who has been employed to make a medical evaluation for one side is called to testify by the other side, lawyers say that he is called as an *adverse witness.* An *impartial medical witness* normally refers to one who is appointed by the court to make an impartial medical evaluation and report which is given to the court rather than to a party to the action."

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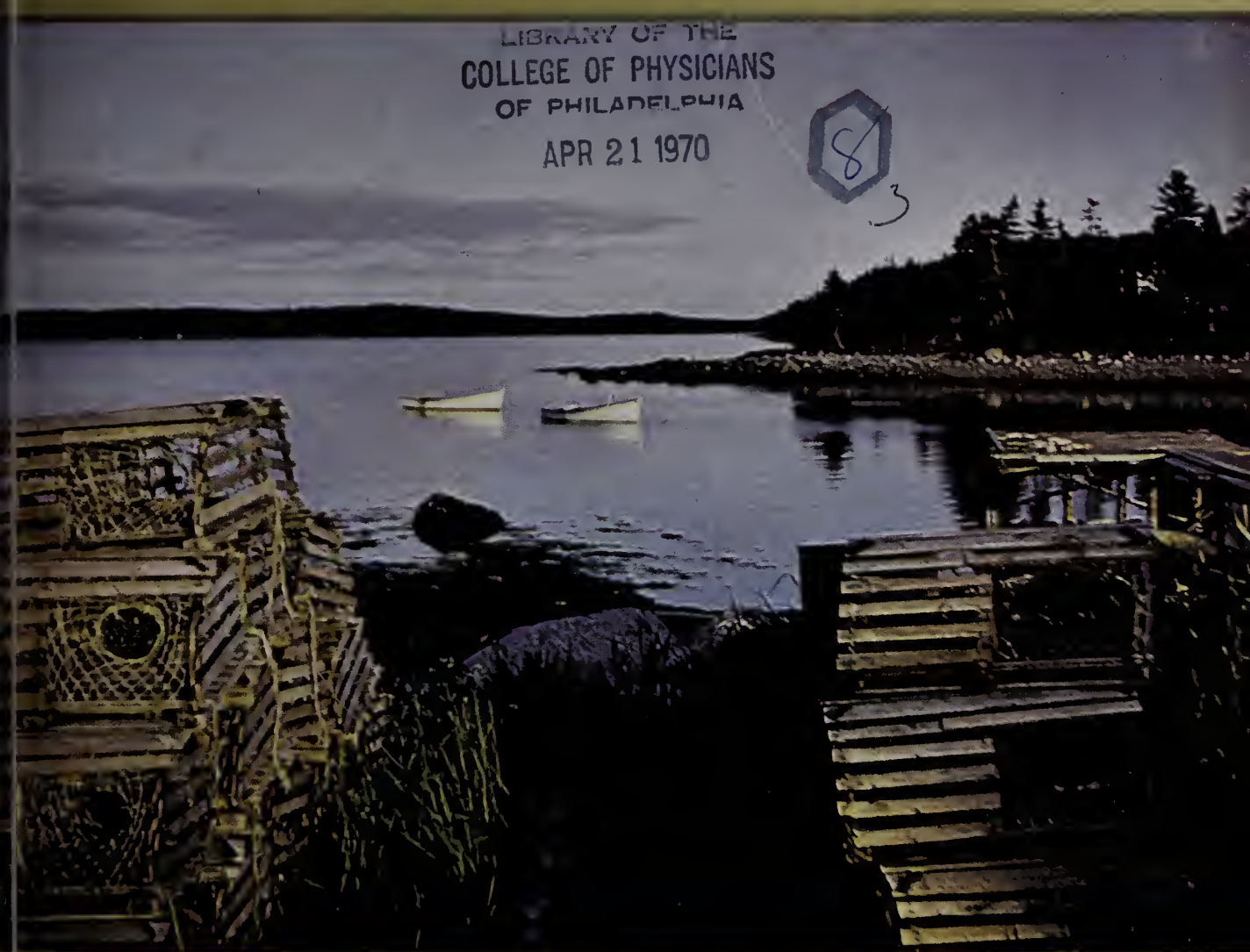
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APRIL, 1970

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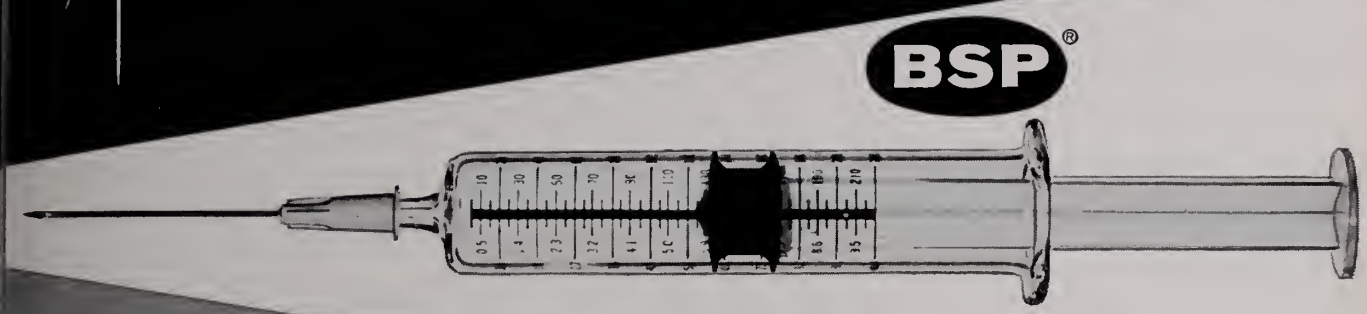
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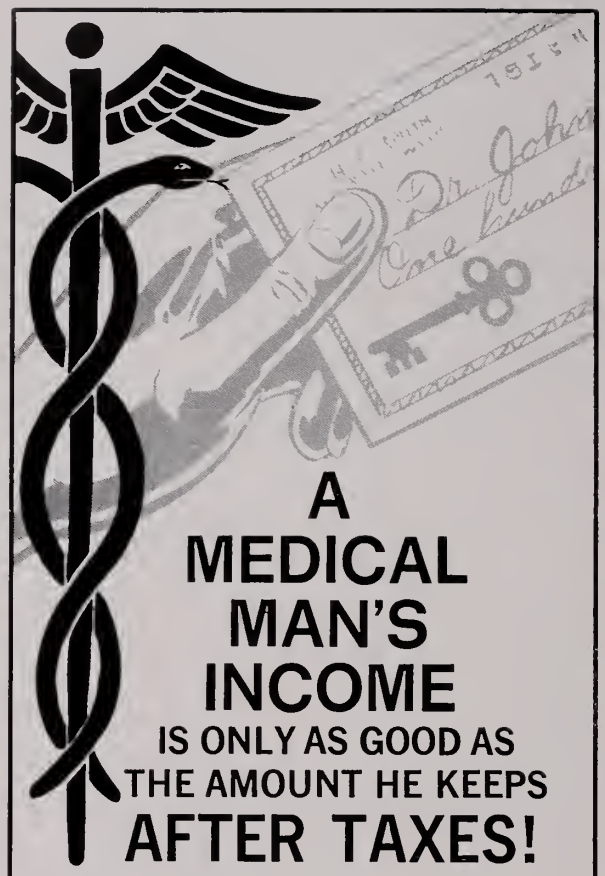
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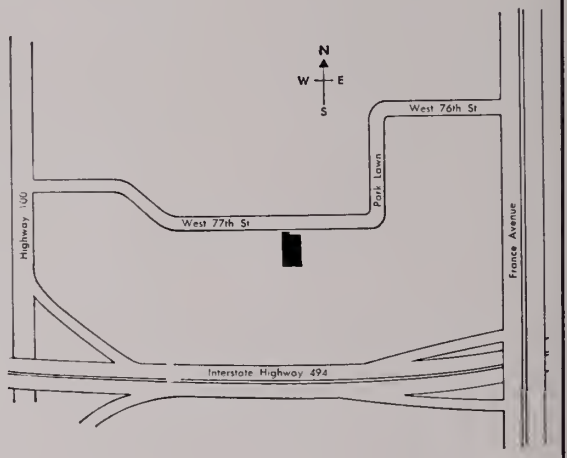
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Meet the President



Delmar R. Gillespie, M.D.

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See the President's Letter, Page 351.



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You might also say that all interns aren't alike, either.







President's Letter

117th Annual Meeting

The council and Officers of the Minnesota State Medical Association extend a cordial invitation to all physicians to attend the 117th Annual Convention of the Association in Duluth, May 18, 19 and 20. This year we have again an excellent and unique program. Because of the multiplicity of meetings doctors are expected to attend, such as the Hospital Staff Meetings, County Society Meetings, General Practice and Specialty Group Meetings as well as National Meetings, together with the practice of medicine, it is difficult for any physician to find time to attend all of them even though he may wish to do so. Combining meetings may be one of the solutions to this dilemma.

This year the Minnesota State Medical Association in cooperation with the Minnesota Heart Association has developed a program that will be of exceptional interest to all doctors. The Committee on Scientific Assembly spent many hours arranging this program and feels that this is one you really cannot afford to miss. The Minnesota Society of Clinical Pathologists have also arranged an excellent program, which you may wish to attend.

All meetings will be held in the Auditorium —Arena Complex in Duluth; if you have not visited this Complex, you must do so.

Monday morning, May 18, papers will present an in-depth study on "Calcium Metabolism." Monday and Tuesday afternoons will be devoted to workshops that will review a number of timely subjects including "The Pill" and "Suction Completion of Abortion." Other topics are even more interesting.

The noon luncheon on Monday is a must. Dr. James F. Martin will speak on a topic every doctor and his wife should hear—"Communication: Physician-Patient; Physician-Spouse," both an educational and humorous subject.

At the Annual Banquet Monday evening, a program will be presented which is entirely different from any we have had in the past. If you miss this program you will forever regret it.

On Tuesday and Wednesday mornings, the Minnesota Heart Association will present a series of papers on "What's New in Heart Disease."

At the noon luncheon on Tuesday "Newer Approaches to Medical Education" will be discussed by Dr. Richard Ebert and may enlighten us as to how we can lick the doctor shortage.

I must emphasize to you that the program this year is outstanding. I urge all physicians to make every effort to attend.

Delmar R. Gillespie, M.D.
President
Minnesota State Medical Association

STATE MEDICAL ASSOCIATION

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Number 4

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Presymptomatic Diagnosis of Breast Cancer*

HENRY PATRICK LEIS, Jr., M.D.†
New York, New York

NEARLY 2,000 YEARS ago Celsus, a Roman scholar said: "Only the beginnings of a cancer permit of a cure," and it is just as true today as then. With proper therapy the cure rate for non-invasive breast cancer approaches 100%; for invasive cancer less than 1 cm. in size the 15-year survival rate is over 80%. Despite all our new refinements in therapy the mortality rate in breast cancer has remained relatively unchanged for the past 40 years. Any improvements reported in the salvage of patients seem to be due almost entirely to early diagnosis rather than to improved methods of primary therapy.

Early Diagnosis

Early clinical diagnosis can be accomplished by patients making monthly self-examinations, by routine periodic examinations by doctors, by cytological examination of nipple discharge, by excision for pathologic examination of all true 3-dimensional dominant lumps, by proper management of the second breast either by random mirror biopsies as suggested by Urban or by delayed, prophylactic, contralateral simple mastectomies in a selected "high-risk" group of patients as I have advocated.

New Diagnostic Methods

MacDonald has emphasized that the average breast cancer has been present for about six to eight years before it reaches the clinically palpable size of 1 cm. If breast cancer is to be diagnosed in a truly early stage, then it is obvious that new diagnostic methods must be used to detect it in this preclinical or presymptomatic stage. Of the numerous procedures that are being employed to do this the ones that offer the greatest promise at the present time are: (1) soft tissue mammography, (2) thermography and (3) xerography.

All these procedures are time-consuming and relatively expensive, and it is doubtful if they could be carried out on the entire female population. An attempt must therefore be made to

*Presented at the Meeting of the International College of Surgeons, Lake Placid, New York, July 4, 1969.

†Clinical Professor of Surgery and Chief Breast Surgery Service, New York Medical College.

pick out the 6% of women who are going to develop breast cancer during their normal life expectancy by clinical and laboratory methods so that they can be studied in detail by these new diagnostic methods.

The High-Risk Patient

The truly high-risk patient from a clinical standpoint would be a Caucasian nun, over 40 years of age, fat and hypothyroid, living in a cold climate in the Western world, who is in the upper socioeconomic group, who has a sister and a mother who have had breast cancer, who has had one breast removed for cancer, who has a premalignant type of fibrocystic disease in the remaining breast, and who has had a cancer of the body of the uterus.

Laboratory Screening Tests

Laboratory tests now being studied as methods to screen out patients with a high risk for breast cancer are: (1) the estriol quotient test of Lemon, (2) the abnormal urinary steroids test of Bulbrook, (3) the buccal sex chromatin anomaly test of Stanley, and (4) the elevated fucose serum glycoprotein test of Rosato.

Mammography

Physical examination, mammography and thermography detect different types of cancers. Their combined use is most important. The value of mammography is not in the differential of benign and malignant palpable lesions but in the detection of nonpalpable cancer.

In a study of 1,626 asymptomatic women over 35 years of age 61 suspicious areas were found on mammography done on a yearly basis for six years and were removed by a segmental resection of that part of the breast. The specimens were then x-rayed to be sure the area of concern had been removed, and this area was marked with needles for the pathologist.

Forty-two cancers were found in 39 women, three being bilateral for a bilateral incidence of 7.7%. These cancers ranged in size from 1 to 9 mm. Thirty-one were invasive and 11, non-invasive. Of the 19 that were benign 13 showed premalignant changes with marked cell atypia. All patients were treated by simple mastectomy with lower axillary gland dissection that showed evidence of cancer, To date there has not been any recurrence of breast cancer in any patient.

This study certainly seems to indicate that it is possible to detect breast cancer in a presymptomatic stage where, with proper treatment, the cure rate can approach 100%.

Cold Weather Stress

A Minnesotan can't write about winter stresses without mentioning the snow shovel. Even when the "big lie" about this implement's deadliness has been laid to rest, it still causes many a sore back and ruined temper. But the snow shovel probably saves many of us from a much worse strain. The exercise people take to wielding the blade, and that they take to keep themselves in shape for it, curbs the much greater threat of *inactivity*. In this age of the automobile, the washing machine, and the television, the greatest stress associated with harsh winters has become "snowbound stagnation." Unless you make a special effort to combat it, you find yourself tiring easily, biting people's heads off at the least excuse, plagued with constipation and other minor ailments—and much more prone to serious disorders than would otherwise be the case.*

*John E. Eichenlaub, M.D.: The Minnesota Doctor's Home Treasury of Unusual Stress Easers, 1964.

The Last Word

The psychiatrist and the priest were discussing their work. The former commented, "Women, Father, will no longer have to confess to you, for they are being psychoanalyzed by me."

"That's possible, Monsieur. But you still cannot pardon them."*

*The Speaker's Handbook of Humor, Maxwell Droke.

Presymptomatic Diagnosis of Cancer of the Pelvis*

SALVATORE R. TRAINA, M.D.†
Medford, Massachusetts

THE NEWER CONCEPTS in gynecological oncology seem to be focused on early case finding and diagnosis and on earlier application of appropriate treatment, resulting in marked improvement in the death rate and in higher five-year survival rates. If we can find these cases of cancer before they become symptomatic, we may improve the survival rates even more.

Etiology

It has been shown that viral nucleic acids in a normal cell subvert the cell's activities into abnormal directions. Whatever alters the karyotype of malignant cells does so without effect on the nearby host cells. This altered karyotype becomes increasingly more abnormal as the malignancy advances.

Dr. N. B. Atkins, a British researcher, has demonstrated chromosomal changes in cells of the cervix manifesting the earliest morphologic signs of carcinoma. He feels that chromosomal changes may help to differentiate between a premalignant and a frankly invasive lesion. Tissue culture techniques are also being used to study these chromosome analyses of premalignant lesions or benign tumors where only small amounts of tissue are available for study. A similarity in karyotypes derived from any single sample of tumor tissue indicates that the cells have arisen from a single chromosomally altered cell. The karyotypes of different tumors vary and, when we find different karyotypes in different sections of the same tumor, it demonstrates a multicellular origin.

As these studies proved, new knowledge may help to check the spread of these malignant cells with antigenic preparations to raise the host immunity to or rejection of this foreign tissue. Another approach may be the preparation of

*See Curbstone Consultations, page 425.

†Chief of Obstetrics and Gynecology, Somerville Hospital; Clinical Instructor in Obstetrics and Gynecology, Boston University Medical School and Vice-Chairman of the Board of Regents and Vice-President, United States Section, International College of Surgeons.

an antiviral vaccine to prevent the development of viral infection and the possible development of cancer.

Because of their location, different cancers of the pelvis have different prognoses. Cancers that are readily visible or accessible, like cancer of the vulva and vagina and of the uterus, are usually found and treated earlier with better results. Ovarian cancer, however, is more difficult to find early. The prognosis, irrespective of the histologic type, varies almost directly with the stage in which the ovarian cancer is found. In stage 1 five-year survival is 69%, but in stage III B, only 15%. The overall five-year survival for all stages is 27%. Although advanced cases that have been treated with either or both radiation and chemotherapy after surgery has removed as much of the ovarian lesion as possible, have shown a slightly improved survival rate, the main hope of better survival figures lies in *earlier* diagnosis. To this end, women must be educated to have adequate annual pelvic examinations along with their Pap smears. This will definitely improve our statistics, as the drop in the death rate of uterine cancer in the last 10 years has shown: from 12.3 to 6.7 per 100,000, down 46%.

Early diagnosis is still the heart of any program for the treatment of any cancer. As women become more cancer-oriented or as larger screening programs become available, then, hopefully, all women will be checked periodically, affording earlier and better treatment.

Cancer of the Cervix

The current concept of viral etiology and our present knowledge of the epidemiology of cervical cancer indicate that cervical cancer is a social disease—a true venereal disease occuring more often in the poor. To determine which are the high-risk patients who should be closely followed so that any cervical cancer can be found in its earliest stages, we should look to several environmental factors.

Environmental Factors

(a) Poor non-whites have twice the incidence of cervical cancer as whites in the same area.

(b) Southern whites have a 67% greater incidence than more well-to-do northern whites.

(c) Lowest-income whites have a 50% greater incidence than highest-income whites. All of the poor groups seem to marry at early ages.

(d) Cancer of the cervix shows a higher incidence in those women who had intercourse at an earlier age or married more frequently.

(e) The frequency of coitus does not seem to be implicated, but number of partners is a factor. One study showed that the incidence among prostitutes was four times that of the general public.

(f) The higher incidence of cervical cancer with excessive child-bearing is associated not so much with the number of pregnancies *per se* as with the fact that numerous pregnancies indicate coitus at an earlier than usual age, especially between the ages of 15 and 17. Prostitutes have fewer children.

(g) The non-use of mechanical contraceptives seems to cause a higher incidence, probably on the basis of greater exposure to smegma or infection and poor hygiene.

(h) Cancer of the cervix is rare in any celibate group like nuns, and also in females married to circumcised males. (Cancer of the corpus uteri is seen in nuns in the same ratio as in the general population.)

(i) There is a direct association in the incidence of syphilis and cervical cancer. There is also an increase of cervical cancer in women who have had repeated marital separations or divorces.

All the above factors tell us where to look for the earliest or presymptomatic cancer of the cervix—namely, in the high-risk individual.

Age

The peak age for cancer in situ of the cervix is between the ages of 35 and 38, and for invasive cancer from age 45 to 48. Cancer in situ is rare in women over 65 years of age.

Screening Programs

British Columbia in Canada has reported a drop in uterine cancer mortality from 11 to 7 per 100,000 after instituting a screening and follow-up program. Their figures also reveal a higher incidence of cancer of the cervix in the poorer groups.

Simple, do-it-yourself mailing kits for Pap smears have provided some good reports; but other valuable information is lacking because of the absence of pelvic examination and the difficulty of obtaining a follow-up report.

In any adequate survey, all class III and IV smears should have adequate pelvic examinations, Schiller testing, and biopsy of suspicious areas. The histology laboratory makes the diagnosis from *biopsy or conization* specimens. If a cervical biopsy reveals cancer, then the next step is to determine if there is invasion. This determination, as indicated by pelvic examination and cold knife conization, is important for adequate staging of the disease so that appropriate treatment can be started. If the biopsy does not reveal invasion, then cervical, cold-knife conization must be done to rule out invasion higher up.

If biopsies reveal dysplasia, which many observers consider a forerunner of cancer in situ, conization is done to rule out an early malignant lesion higher up. Adequate cauterization of the cervix well beyond the area of dysplasia may prevent progression to malignancy. It is the finding and treating of these early pre-malignant or pre-symptomatic lesions that has lowered the mortality rate and prolonged survival. A study at the Los Angeles County General Hospital on 90,000 pregnant women disclosed an incidence of cervical dysplasia of 5 per 1,000 and of 3 per 1,000 for carcinoma in situ. This is about equal to the rate reported in non-pregnant women. Conization was done only in "obvious cases" of cancer of the cervix in these pregnant females to properly stage the disease and decide on treatment.

The cytological information gained from atypical cervical and vaginal cells in Pap smears can aid in the detection of infection, nutritional deficiency or the estimation of hormone production, thus adding helpful information in the adequate treatment of gynecologic patients.

Incidence and Survival

Adequate screening in the search for the early case of cervical cancer is reflected in the following two studies. In Norway, screening programs were carried out on 46,400 females, 25 to 59 years of age, in 1964 and in 1967. The in-situ and invasive carcinoma ratio is indicated in the Table.

The results of two separate five-year time-period studies, done at the University of Texas, M. D. Anderson Hospital and Tumor Institute, are illustrated in the Table.

Cancer of the Body of the Uterus

Cancer of the endometrium is about one third to one fourth as common as cancer of the cervix. It must be remembered that in most cases the diagnosis is made in patients already showing signs and symptoms. Clyde Randall has expressed the belief that uterine cancer must, in most instances, exist in a detectable stage for several years. This implies that routine cytologic smears and biopsy or curettage in any suspect case would reveal many more early endometrial lesions which could in turn provide earlier treatment with a better survival rate. Most clinics report a five-year survival rate in 60%

TABLE
Incidence of Cancer

	In Situ	Stage I	Stage II	Stage III	Stage IV
1944-1949	1.2 %	9.5%	34%	32%	15%
1960-1964	19.1%	21.1%	26%	18.6%	4.4%
		Total 5-Year Survival Rate			
1944-1949	66.7%	83.4%	48.8%	28.3%	0.0%
1960-1964	92.7%	84.8%	67.1%	37.4%	8.1%

of their patients. A high index of suspicion is important in the pre-symptomatic diagnosis of cancer.

Epidemiology of the High-Risk Group

Epidemiologically these patients seem to have a similarity in body habitus.* They are usually *menopausal* and above 50 years of age, though over 35% of women who develop adenocarcinoma of the endometrium had regular periods beyond the age of 50. Most patients have a history of *post-menopausal bleeding* (15%) or a background of previous *menorrhagia* or *dysfunctional bleeding.* Statistics reveal a high association of obesity, hypertension, diabetes and biliary tract disease. These women commonly have a history of infertility or menstrual disorders which imply a possible basic endocrine dysfunction.

Diagnostic Procedures

Although postmenopausal bleeding should be investigated in all women by adequate curettage, any suspicious enlargement of the uterus, unexplained spotting or leucorrhea should be suspect and have endometrial lavage, aspiration of the fluid, spinning down of the cells, and cytological study to reveal the diagnosis. Occasionally a limited sample of endometrium may be obtained early and painlessly in the office with a small curette, though curettage under anesthesia not only rules out any early growth or benign polyp, but allows an adequate "inspection" of the endocervical area.

A pathological diagnosis of cystic or adenomatous hyperplasia of the endometrium is considered a pre-malignant lesion and should be treated. Occasionally a patient on continuous estrogen therapy without opposing androgen therapy may present a confusing endometrial pattern. Such a patient should be taken off medication and a repeat curettage done four to five weeks later.

Some patients with endometrial cancer give a history of previous radiation therapy, which was once common for menometrorrhagia.* Although the association is definite in this group, there is still some question as to whether the radiation stimulated the growth or whether the patient had predisposed endometrium, which Arthur Hertig calls "vulnerable substrate."

Curettage should be done before any pelvic laparotomy to rule out an unsuspected cancer of the cervix or uterus which could alter the treatment planned. If an early endometrial cancer is found, the cervix should be sutured prior to hysterectomy to prevent spillage of malignant cells into the pelvis. The presence of endometriosis, adenomyosis, or fibroids is not a predisposing factor.

Treatment

As soon as the diagnosis of endometrial cancer is made, the modality of treatment must be individualized. Early cases respond favorably to total hysterectomy and bilateral salpingo-oophorectomy alone or to preoperative intrauterine irradiation followed by hysterectomy and removal of the adenexae six weeks later. Any local nodes should also be excised, if possible, as well as an adequate cuff of vagina. Once cancer of the endometrium has progressed beyond the uterus, its spread is unpredictable. Occasionally the Wertheim operation has been done with some improvement in survival rate, but the morbidity is increased. Overall, irradiation and surgery have produced up to 80% five-year survival. Postoperatively these patients should be followed over a long period because of their cancer's characteristically slow growth rate.

Recently, luteinizing hormones have been used in large amounts to treat recurrences, metastases and inoperable cases, with improvement noted in 33 percent of patients.

Other Cancers of the Uterus

Sarcomas, carcinosarcomas and sarcoma Batryoides are seen, but less frequently. Treatment for these is complete surgical removal since radiotherapy has not been effective. The treatment of choriocarcinomas has so improved in the past 10 years with chemotherapy that this group of patients has the highest five-year survival rate. It must be remembered that all these latter tumors may spread through the blood stream.

Ovarian Malignancies

Most ovarian masses, with the exception of

*See Test Your Word Score, page 415.

theca cell, granulosa cell and arrhenoblastoma present no symptoms until they become so large as to be visible as an abdominal bulge or cause pressure or obstructive signs and symptoms.

Diagnosis

Early diagnosis depends on a high level of suspicion. We must again look for the high-risk patient. Ovarian cancer patients give a more frequent history of heavy menstrual bleeding and earlier menopause. Also, there are differences in the rates of incidence among ethnic groups; for example, Jewish women have a higher rate than others in the United States and Japanese women who migrate here have a higher rate than their sisters in Japan. Some observers attribute this to higher fat consumption by these women.

Culdocentesis has received a great deal of attention lately in some centers, along with aspiration and examination of peritoneal fluids. There are six common cell groups found in relatively stable proportions in the fluid of healthy young females. This proportion changes with various disease states as well as with the various times the fluid is drawn, e.g., phase of menstrual cycle, postmenopausal state, pregnancy and puerperium. Not only may examination of the fluid reveal exfoliated tumor cells early to help in the diagnosis even before the tumor can be felt; but after operation it may be useful in detecting recurring ovarian cancers. An increase in fluid amount and mesothelial cells may warn of recurrence.

Occasionally attention may be focused on a tumor mass when it shuts off its blood supply by twisting on a pedicle or when sudden spontaneous hemorrhage occurs in the tumor mass. Since the pelvis is very spacious, a tumor mass can reach a very large size—similar to a term-size fetal head—before it is noticed, and by that time it may have become incurable. This is why five-year survival statistics of ovarian cancer are so poor—up to only 27% for all stages. The fortunate woman is the one in whom an ovarian mass is accidently discovered early or is found during a yearly pelvic examination or at the time of an abdominal operation. This fact reinforces the opinion that along with the annual Pap smear, all adult females should have an annual pelvic examination. Those growths which start as malignant growths, as well as those benign tumors which develop malignancies, can then be excised at an earlier stage, possibly before extensive metastases occur. When the metastases are found early, they too can often be more completely removed.

We in the Boston area have arbitrarily chosen 5 cm. as the ovarian tumor size which should be explored. This does not mean that smaller ovarian tumor masses, especially if solid, will not be explored if rapid growth or other signs or symptoms warrant. Even if the tumor mass turns out to be a small dermoid, this allows the dermoid alone to be resected and the preservation of some normal ovarian tissue, which is important since dermoids very commonly are bilateral.

Even *small cysts* can be resected and examined, keeping in mind that serous cystadenoma has a greater chance of being malignant than other cysts, and pseudomucinous cystadenomas have a tendency to be bilateral.

Careful examination at the time of operation should be made for metastases, papillary projections and unusual attachments or extensions to nearby organs. The so-called "simple cysts" are just that and are easily recognized at operation.

Endocrine Influence

The previously mentioned granulosa or theca cell tumors cause *feminization;* the arrhenoblastoma cell tumors, on the other hand, first defeminize, then *masculinize* at an early stage so that they can be found as *small* solid ovarian tumors. If hirsutism has existed for a long time, careful history-taking may reveal a familial origin which may, therefore, not be significant in the diagnosis. About one tenth of granulosa cell tumors or theca cell tumors are malignant; but these are the rarest of the solid tumors.

Dysgerminomas are the most common, usually solid tumors; but they are not endocrine-producing tumors. However, about one third of these are malignant and usually appear in late adolescence. Most malignant ovarian tumors are primary cystic tumors.

Unmarried females show a higher rate of ovarian cancer than married females, a fact which may be attributed to *hormonal changes*

resulting from pregnancy. In women over 40, more than half of all ovarian tumors are malignant. Malignancy should be suspected in ovarian growths that show recent hemorrhage, papillary projections into the lumen, extension to nearby organs or solid cystic tumors.

Treatment

Malignant ovarian tumors should be treated with total *hysterectomy, bilateral intact salpingo-oophorectomy and omentectomy*. Radiotherapy, except for palliative treatment, has little therapeutic value except in dysgerminomas. Appropriate chemotherapy will produce subjective and objective tumor remission for 1 to 1½ years in at least half of these patients.

In those patients in whom there is doubt about the malignancy of the ovarian mass, conservative surgery should be done; if malignancy is established by the pathologist, the abdomen should be reopened and definitive treatment carried out regardless of the patient's age. *Only unilateral granulosa-theca cell tumors* may be treated adequately by unilateral oophorectomy to avoid needless castration. Thorough history-taking and adequate medical investigation will aid in the diagnosis. This should be part of the annual pelvic examination.

Not For Dogs!

Another chemist with whom Bernard collaborated during the early years of his career was Charles Barreswill. . . . Barreswill was in the habit of drinking cognac brandy after every meal. It was an aid to digestion, he said. Although Bernard came from one of the great wine regions of France, was descended from a long line of winegrowers, and was a total abstainer himself, Barreswill's drinking upset him.

As for the idea that cognac was an aid to digestion, Barreswill had come to the wrong man with that particular excuse. Bernard was eventually to devote a substantial part of his lifework to determining what happened to various substances taken in as food.

Bernard decided to perform an experiment to test Barreswill's contention that cognac promoted digestion. He would feed a dog and then give it a substantial amount of cognac. Then he would open the dog's stomach to see how well the food was being digested.

"I wish you would just give *me* the drink," Barreswill protested.

Bernard went ahead with the experiment. He found that cognac did not improve the dog's digestion, but actually impaired it; some of the food in the dog's stomach had not been digested at all.

"What do you think of that?" Bernard asked his friend triumphantly.

Barreswill thought for a moment. "What your experiment proves," he said, "is that cognac was not meant for dogs."*

*Jerome Tarshis: Claude Bernard, Father of Experimental Medicine, 1968.

Overworked

The doctor, driving up to a homestead to deliver the family's 11th child, said to the father when he opened the door, "I almost ran over a duck out there—is it yours?" "That's no duck," sighed the man. "It's the stork with its legs worn down."—Harold Helfer

One machine can do the work of fifty ordinary men. No machine can do the work of one extraordinary man.—Elbert Hubbard

Cryogenic Applications in Neurosurgical Practice

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FOR MORE THAN A century there have been sporadic reports indicating the potential usefulness of cooling or freezing biologic tissues to produce controlled physiologic inhibition or anatomic destruction. Heretofore, however, the lack of adequate instrumentation has prevented the realization of the potential value of extreme cold as a surgical tool. In recent years, there have been classic advances in cryogenic engineering to the point at which the application of cryogenics to surgery will be limited only by the imagination of the surgeons and their interest in investigating this new approach.

It is the purpose of this report to summarize some of the cryogenic applications in neurosurgical practice.

Cryogenic Instrumentation

In the cryogenic system[1] the source of refrigeration is liquid nitrogen, the temperature of which is dependent upon the pressure. At 22 pounds per square inch, liquid nitrogen is stored in this system at −196° centigrade and delivered from a vacuum-insulated storage tank through the delivery tube. This process serves to pre-cool the feeding tube to the temperature of liquid nitrogen, thereby facilitating its maintenance in liquid form. After the tube has been sufficiently pre-cooled, the liquid nitrogen is permitted to enter the cannula. The cannula is fully insulated by means of a vacuum except for 3 mm at the tip, thus permitting the tip to reach predetermined temperatures, ranging from 0° centigrade (for purposes of physiologic testing) to −196° centigrade for lesion creation of various sizes. The standard cannula, measuring 2.2 mm in diameter, is capable of producing a predictable, sharply circumscribed lesion ranging in diameter from 3 to more than 10 mm in diameter. Larger lesions can be readily produced by two or more applications of the probe. Various probes of different sizes and shapes may be employed with the same basic cryogenic system to produce lesions of any desired volume or shape.

Cryothalamectomy for Dyskinesia

Since 1961 more than 5000 individuals have been subjected to cryothalamectomy for the relief of abnormal movement disorders, namely: Parkinson's disease, intention tremor, dystonia musculorum deformans, torticollis,

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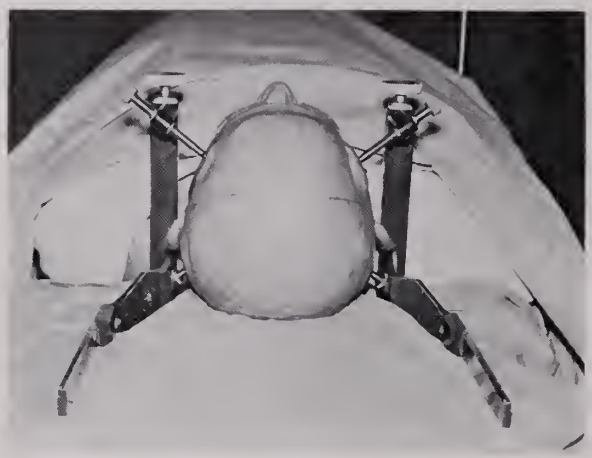


Fig. 1—Head of a patient fixed to the head-holder.

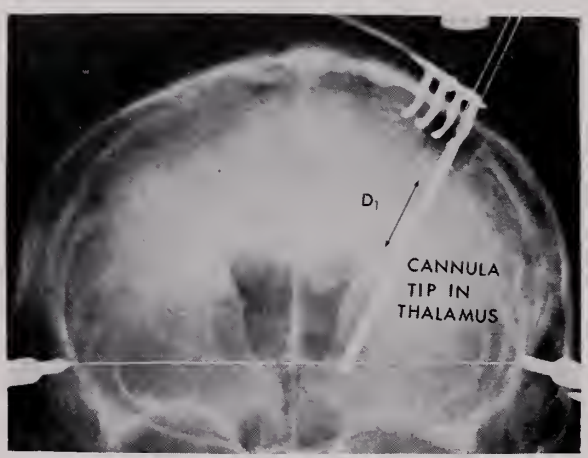


Fig. 2a—Anteroposterior and lateral ventriculogram, with the cannula already placed in the target area (ventrolateral nucleus of the thalamus).

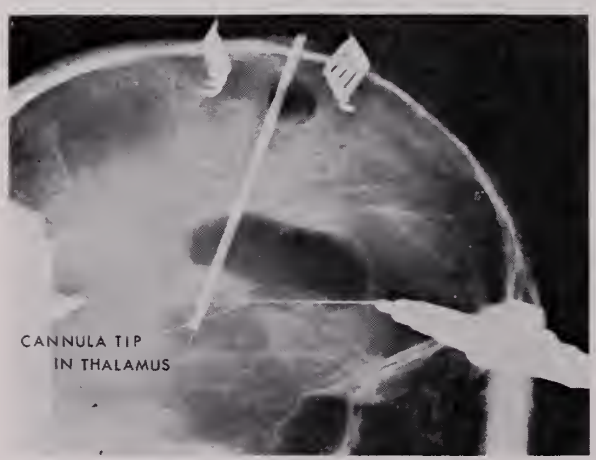


Fig. 2b.—Lateral ventriculogram.

chorea, athetosis, ballismus* and myoclonus. The surgical target of choice lies within the lateral mass of the thalamus, being centered in the posterior portion of the ventrolateral nucleus and the anterior portion of the ventroposterolateral nucleus. Cases of torticollis usually require additional lesions in centromedianum and bilateral surgery before achieving good, lasting results. The same holds true for dystonic patients if the deformity involves the head and neck. Patients with involuntary movement disorders are operated upon without premedication or general anesthesia.

Procedure

The head is fixed to the operating table in a special head-holder (Figure 1). A small trephine opening, the size of a dime, is made at the level of the coronal suture, 3 to 4 cm from the midline. Ventriculography is performed to localize the target area. The cryosurgical cannula is guided to the ventrolateral nucleus of the thalamus under x-ray control (Figure 2). The tip of the cannula is then cooled down to −10°C for 30 to 60 seconds. During this period, the effect of a lesion can be observed, thus providing a clinical-physiologic check of the correct surgical localization of the cannula and enhancing the safety and certainty of the procedure. The temperature at the tip is gradually lowered to −70° or −80°C, so that the lesion is gradually enlarged while the patient is being observed. In this way, a lesion approximately 7 to 8 mm in diameter is produced. Figure 3 illustrates the size and site of a cryogenic lesion in the human thalamus.

*See Test Your Word Score, page 415.

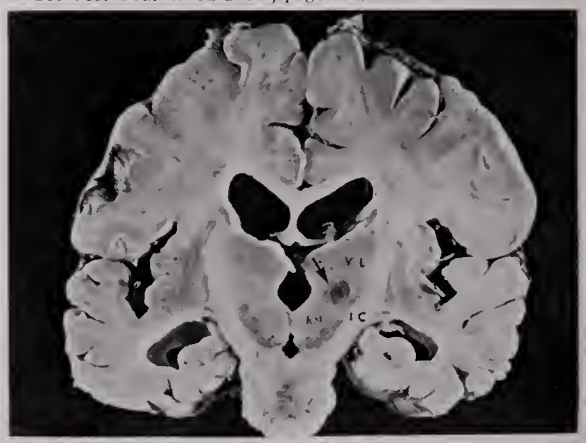


Fig. 3—Cross section of a patient's brain subjected to stereotaxic thalamic surgery. The cryogenic lesion is well placed in the ventrolateral nucleus of the thalamus.

Results

The results of cryothalamectomy in the case of *Parkinson's disease* indicate that tremor and rigidity are relieved in approximately 90% of cases.[2,3,4] The procedure, being safe, has enabled us to extend it to elderly patients: 40% of ours being over 60 years of age, and 10% over 70 years.[5] Other poor-risk patients, such as those suffering from diabetes mellitus and hypertension, are now operated upon. Formerly these patients were not considered surgical candidates and were denied surgery. Even with extension of this procedure to these poor-risk patients, the mortality is only 1.2%; and that of cerebral hemorrhage, secondary to surgery, is 0.8%. This represents almost a 50% reduction as compared to chemothalamectomy where mortality was 2.3% and cerebral hemorrhage 1.7%.[6]

Intention tremor is equally relieved with cryothalamectomy. In 1960, one of us (Cooper)[7] postulated that "intention tremor is due to pathologic lesions anywhere between the ipsilateral dentate nucleus of the cerebellum and the contralateral red nucleus. This results in impaired feedback of proprioceptive sensory information from the muscle spindles to the cerebral cortex via the dentato-rubro-thalamocortical fibers. A surgical lesion within the ventrolateral nucleus of the thalamus would block the faulty information from reaching higher centers, thus relieving the tremor." A recent review[8] of 73 consecutive cases of intention tremor of diverse etiology (familial, multiple sclerosis, post-traumatic, posterior fossa tumor, etc.), operated upon on our service, has shown that more than 90% of the cases were relieved of their tremor. This corroborates our previous findings[9,10] as well as those of others.[11,12]

Torticollis has been helped in many cases by thalamic surgery;[10] however, the results are not as spectacular as in intention tremor or parkinsonism. Approximately 75% of the patients are improved by this type of surgery.

Dystonia musculorum deformans, a rather severe disabling dyskinesia of children, has been effectively treated with cryothalamectomy.[13] Between 1954 and 1966, we operated upon 144 dystonic patients. Of these, 47 have undergone surgery in one hemisphere, while 97 had bilateral basal ganglia surgery. In 16 patients the globus pallidus was the surgical target, while in 128 the thalamus was the site of surgical intervention. Seventy-seven percent of our total series of dystonic patients have achieved long-standing reversal of their symptoms following surgery; the symptomatic relief and the functional result were good to excellent. In the remaining 23% of the patients, recurrence of symptoms or failure of surgery to reverse the dystonic symptomatology was observed. This latter group includes four patients (2.7%) who died following operation.

Other types of involuntary movement disorders (*chorea, athetosis, ballismus and myoclonus*) can also be treated through the same surgical procedure, although the results are less certain.

Cryothalamectomy for Pain

The thalamus serves as a relay for the spinothalamic and quintothalamic fibers. It is believed that crude pain becomes consciously perceived at the thalamic level. Several investigators[14,15,16] have attempted to attack certain pain syndromes such as thalamic pain, phantom-limb, atypical facial pain, causalgia, and the pain of malignant disease, by making lesions in different thalamic nuclei. The procedure is carried out in the same manner as for the dyskinesias, except for the necessity of placing multiple lesions. Recent statistics have shown encouraging results, almost 60% success.

Freezing of Brain Tumors

We have investigated the application of cryogenic techniques to brain tumors,[17] both deep and superficial, including gliomas, meningiomas, angiomas and metastatic tumors.

In the case of the deep brain tumors, direct surgical attack is either impossible, or, if it is attempted, the destruction of overlying brain tissue leaves the patient with catastrophic neurologic sequelae. It appears, however, that cryogenics has now opened new avenues for the surgical treatment of these inoperable tumors. Through the use of brain scanning and serial angiography, the size and site of the tumor is determined. With the patient's head

positioned in the head-holder, the cryogenic probe may be placed stereotactically within the center of the tumor (Figure 4). The neoplasm can then be destroyed from the center to its periphery. Some tumors, because of their small size and their depth below the surface, can be left to necrose in situ following cryogenic treatment. Larger and more superficial tumors require evacuation of the necrotic tissue, a few days after freezing, and this can be easily achieved through gentle suction.



Fig. 4—Cryogenic probe, placed in the center of a deep frontal glioma.

Superficial brain tumors, such as meningiomas, are exposed by standard craniotomy procedures. The probe of adequate size is then placed in the center of the tumor and the tumor frozen to its estimated size. Removal can then be achieved either by blunt dissection or by using a high-speed drill (Figure 5). The patients seem to tolerate the freezing technique much better than routine removal, demonstrating a more benign postoperative course.

Walder explored the possibilities of thrombosing vascular anomalies of the brain, using freezing with encouraging results.



Fig. 5—Meningioma frozen solid by the cryogenic technique. The air drill is used in removing the frozen tumor.

Cryohypophysectomy

The main indications for removal or destruction of the pituitary gland are primary tumors within the gland, diabetic retinopathy and metastatic carcinoma of the breast or prostate. The routine transfrontal approach for hypophysectomy demonstrates its own mortality and morbidity; however, with the transsphenoidal approach,[18] the surgical risk is negligible and the patient is spared a great deal of postoperative discomfort. The operation is performed by fixing the head in the head-holder and, with a stereotaxic guide, passing the cryogenic probe through the nostril, the sphenoidal sinuses, the floor of the sella turcica into the pituitary gland (Figure 6), which is then frozen at −180°C for 10 minutes. The same procedure is repeated through the other nostril.

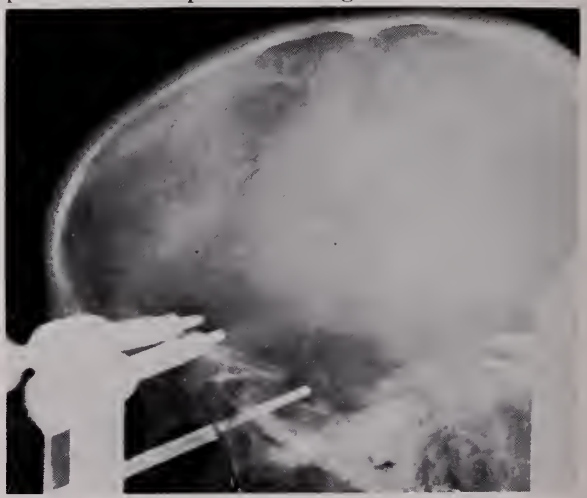


Fig. 6—Cryohypophysectomy: The cryogenic probe 2 2 mm is seen inside the sella turcica.

Behavior Disorders

Several surgical procedures for the treatment of intractable psychosis were introduced a number of years ago. The most prominent are prefrontal leucotomy, orbital undercutting, fornicotomy, cingulotomy and amygdalectomy. With the use of the cryogenic probe, these procedures can be done stereotaxically* with relative safety.[19]

*See Test Your Word Score, page 415.

Epilepsy

The cryogenic probe has also been used in the treatment of epilepsy. In cases of temporal lobe epilepsy, it has been possible to delineate the epileptogenic focus by means of implanted electrodes, and to destroy this with a stereotactically placed cryogenic lesion. More recently, Jinnai et al.[20] and Mullen[21] have demonstrated that epilepsy of a more diffuse nature can be altered or abolished by placement of stereotactic lesions within the thalamus.

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Courage

Many people ignorantly think that whiskey will give them courage, for after a few drinks of liquor, they shed their stage fright and do many things they wouldn't dream of performing while sober. But alcohol never produces courage! It only lowers mental age to the point where the drinker is childlike and thus no longer realizes the gravity of the situation. He is actually feebleminded, temporarily!*

*Dr. George Crane: The Quotable Dr. Crane, 1968.

Study until twenty-five, investigation until forty, profession until sixty, at which age I would have him retired on a double allowance.—William Osler

Religion and the Law

Vaccination

MANY ETHICAL PROBLEMS confront physicians and medical investigators. Some of these are quite new and others have acquired larger dimensions in recent years, both because of advances in medical science and because of the increase in support for medical research.

One type of new problem for practicing physicians which I should like to call to your attention is one in which a conglomeration of scientific judgment and prediction, and of ethical judgment and presupposition is involved. I refer to the current dilemma facing physicians regarding vaccination against smallpox in the United States today. This virus disease has been practically wiped out in this country. Such a large fraction of the population has been immunized against it that there are no endemic reservoirs of the virus in the country. Deaths from smallpox in the United States now approach zero. However, serious disease and several deaths occur annually from smallpox vaccination, because in a very few instances, one in several hundred thousand, the modified virus used causes an encephalitis, potentially fatal.

The scientific prediction is that if the current practice of virtually universal vaccination against smallpox were discontinued, there would be within a generation an epidemic of smallpox which would cause many millions of deaths and untold suffering. However, it can also be predicted that so long as most persons are immunized against the disease, a particular non-immunized individual would have practically a zero chance of contracting it.

The pediatrician caring for an individual infant therefore confronts a dilemma. He says to himself, correctly: if I vaccinate this child the risk of death from that act is many times greater than the risk of dying from smallpox, so long, of course, as most other children are vaccinated. Some physicians have chosen not to vaccinate their patients on the grounds that their duty is to their individual patients, not to society or to the next generation.

My own reaction to this apparent dilemma, which is currently being vigorously debated, is to insist that the health and welfare of the larger society take precedence over the interests of the individual and that, so long as the threat of a plague hangs over an unvaccinated population, it is unethical for a physician to fail to recommend vaccination against smallpox. I hasten to add, however, that it is the duty of the larger community to promote and support liberally those types of scientific research which might lead to a real solution to the problem. The ethical dilemma would vanish if one of three possible advances could be made: (1) a modified virus could be produced which was never neurotropic in its action; (2) a method could be employed at the time of vaccination to prevent invasion of the central nervous system; or (3) a satisfactory treatment for the encephalitis could be developed.

I should like to emphasize this moral obligation of society because the support of medical research is ordinarily regarded by the public as having purely utilitarian objectives. Hence I want to stress the moral imperative to support research in this and in many other cases.

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Minneapolis, Minnesota

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Supported by the Louis W. and Maud Hill Family Foundation.
See Part II in the May issue.

Microsurgery

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THE DEVELOPMENT of microsurgery represents a phase of the endless search for perfection in suturing techniques. Interest initially was stimulated in vascular surgery, particularly in coronary disease. Subsequently, various forms and degrees of the technique have been applied to such other structures that neurosurgery has more recently become the discipline most interested in the problem. The rationale for microsurgery was to provide a means through improved optics (hence, vision) so that the accepted principles of vascular suture could be exercised more accurately and more discriminatively. Subsequently, as microtechniques were utilized with greater frequency, the rationale was modified to a more logical perspective in which vessels of a critical nature and of a small diameter, 2 mm or less, could be successfully sutured. To date the disciplines in which this technique has the most promise are in neurosurgery and in some aspects of neonatal surgery.

Microvascular (Microangeional) Surgery

Surgery of the small vessels has continued to be the area of greatest activity. The term microvascular or microangeional is somewhat of a misnomer since the vessels are grossly visible. The term refers more to microtechnique in blood vessels since visualization, and hence surgical technique, is greatly enhanced by the use of optic systems for enlargement. In order to permit the technique to be utilized, it was found that the customary instrumentation available, including the more recently developed vascular instrumentation, was woefully insufficient. An entire new spectrum of instruments had to be developed, spearheaded by Jacobson.

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Dr. Blair is now Professor of Surgery, University of Colorado Medical Center, Denver.

Problems to Surmount

The Deterrent of Tremor

Several deterrents had to be overcome, one of which was the natural tremor, which always seems to increase as the surgeon approaches the site for suturing. The disaster encountered in a 1-mm blood vessel from tremor is obvious. Special holders were developed so that the vessel could be held completely still. Similarly, the surgeon had to learn to utilize several means for restraining his tremor.

Suture Material

Other factors included the problem of the sutures themselves, particularly the point at which the suture was affixed to the needle. Too often the needle proved to be of a greater diameter (vastly greater under a microscope) than the suture itself. The smaller vessels are more muscular than the larger ones and, therefore, more susceptible to vasospasm. The causes of failure are listed in Table 1. The insufficient flow is primarily due to the vasospasm as well as to the luminal narrowing. The suture material had to be placed very carefuly; otherwise it protruded into the lumen causing narrowing. Infection proved to be a serious problem in initial studies but has recently been overcome. Reports vary considerably with respect to the results as judged by the patency of a vessel within several months after suturing. In Vermont several workers, including Donaghy and Yasargil, were able to acquire a 68% patency in vessels exceeding 1 mm, but only a 31% patency in those less than 1 mm. These usually were femoral vessels of cats. With modification of techniques, however, particularly addressed to the matter of spasm and to insufficient flow, there has been considerable improvement, as noted in Table 2. It is interesting that the fundamental technique of end-to-side anastomosis even in small vessels proved to make considerable difference in the results. In vessels less than 1 mm in diameter, it was found that end-to-side anastomosis yielded a 70% patency rate as compared to only a 50% rate with end-to-end anastomosis. T-tube bypass proved to be extremely useful in vessels 1-2 mm in diameter.

TABLE 1
Microangeional Surgery Causes of Failure

Insufficient flow	Luminal suture
Lumen narrowing	Infection
Foreign material	Spasm

TABLE 2
Microangeional Surgery

Vessel Size	Technique	% Patent
1-2 mm	End-to-end	50
1-2 mm	Patch	80
0.5-1 mm	End-to-end	50
0:5-1 mm	End-to-side	70

Clinical Trials

Intracranial Vessels

Clinical trials have not been as uniformly successful, and no operator has a very large series. Nevertheless, it has been possible to reconstruct smaller vessels within the cranium with some degree of success. At the present time, the clinical applicability of this technique remains within the investigation area, awaiting considerably more experience. Generally the patients in whom this technique is applied are those who would fall into a category of salvage; therefore, while the overall results are not very striking at this time, the important point is that at least a few individuals who would have suffered paralysis or greater disasters have been spared.

Neural

Peripheral nerve surgery has progressed to a point where the results are generally considered to be fairly satisfactory. On the other hand, while motor function can be restored provided the conditions are ideal, sensory function remains at an unsatisfactory level. One of the reasons for this problem is that the suturing technique lacks appropriate orientation in the varying nerve fibers.

In a series of cats studied in our laboratory, three different techniques were employed: epineural with no operating scope, epineural with the operating scope, and a more definitive fascicular using the operating scope. Several

months later it was noted that conduction time was absent in five or six animals with epineural suturing using no scope and was prolonged in one. Utilizing the scope, there was no conduction time present in four of eight animals, while in the other four, conduction time proved to be prolonged, varying from .7 to 1.6 msec, with the normal being .4-.5 msec. In animals in which a definitive fascicular approximation with the scope was performed, there was no conduction time in three of 10; in two of 10 it was within normal limits, and in the other five, it was prolonged 7 to 2.0 msec. Therefore, from the physiological standpoint, fascicular approximation with the scope proved to be the most effective means of maintaining some response.

Morphological analysis was also carried out (Table 4). It was noted that utilizing the conventional technique with no operating scope resulted in the greatest degree of tissue reaction with fibrosis. Axonal continuity of an adequate degree was present in three of six with the conventional type, five of eight with the epineural, and eight of 10 with the fascicular approximation with the scope. Identification of myelin and of axons was noted to be greater with the fascicular microtechnique using the scope. While there have been no clinical reports as yet on this, the investigative work suggests strongly that the proper spatial orientation of the structures within the peripheral nerve should result in a far superior result.

Conclusion

It may be argued that microsurgery is a poor substitute for unskilled vascular surgery. This is a poor argument. Microsurgery is designed for areas and circumstances not readily available to macrovision. Much needs to be done investigationally to define its proper role.

TABLE 3
Microsurgical Neurorrhaphy

Technique	Conduction Time (msec) Control	3 Months	% Control
A. Epineural No scope	0.4 -0.5	None (5/6) 0.8 (1/6)	49%
B. Epineural Op. scope	0.4 -0.5	None (4/8) 0.7-1.6 (4/8)	16-63%
C. Fascicular Op. scope	0.35-0.45	None (3/10) 0.4 (2/10) 0.7-2.0 (5/10)	32-63%

TABLE 4
Microsurgical Neurorrhaphy

Technique	Fibrosis	P	Distal Segment* Myelin	Distal Segment* Axons	Axonal† Continuity
A. Epineural No Op. scope	2.2±0.7		2/6	1/6	3/6
B. Epineural Op. scope	1.4±0.6	.05	2/8	3/8	5/8
C. Fascicular Op. scope	1.0±0.5	.01	6/10	8/10	8/10

* = 3 + to 4 +
† = 2 + to 3 +

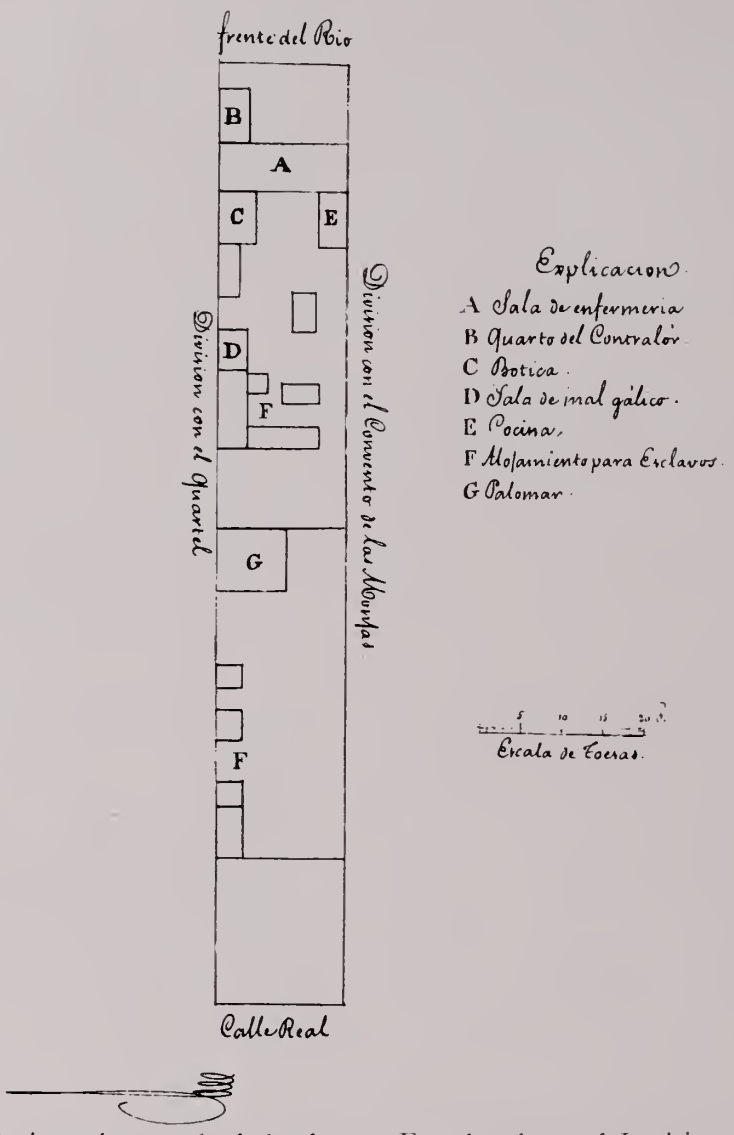
Shakespeare: Medicine

Old Age—"Do you set down your name in the scroll of youth, that are written down old with all the characters of age? Have you not a moist eye, a dry hand, a yellow cheek, a white beard, a decreasing leg, and increasing belly? Is not your voice broken, your wind short, your chin double, your wit single, and every part about you blasted with antiquity, and will you yet call yourself young? Fie, fie, fie, Sir John."

—Chief Justice to Falstaff in Henry IV, Part II:1,2.

Historic Hospitals

The Royal Hospital of New Orleans During the Spanish Period



When Spain took control of the former French colony of Louisiana in 1769, the transfer of public property included the first hospital in the Mississippi Valley, the Royal Hospital of New Orleans. The French had operated a hospital in New Orleans since 1722, and under the Spanish Crown the institution continued to function in the same buildings. The Plan of the Hospital shown here is a copy from the 1769 inventory made later in Havana by Juan Nepomunco de Arocha.

In 1770, the Ursuline nuns who had operated the hospital under the French since 1726 withdrew, leaving care of the colony's sick entirely to the Spaniards. In the years that followed, the Spanish government made some improvements in the physical plant, the most important being a second story added to the main building.

Regulations concerning management of Royal Hospitals in Colonial Spanish

(Continued to Page 402.)

Chemotherapy*

Changing Concepts in Therapy

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THE FIRST REPORT of a chemical agent that is effective when used systemically appeared in 1895, when Lissauer described marked improvement in a patient with leukemia following the use of potassium arsenite or Fowler's solution.

The modern era of temporarily effective clinical cancer chemotherapeutic agents began in 1946 when nitrogen mustard and urethane were first used and found to be effective.

Chemotherapy Agents

The cancer chemotherapeutic agents of value today in the temporary control of disseminated neoplastic diseases in human beings are grouped roughly into six categories.

Antimetabolites

The antimetabolites are substances which compete with the action of normally occurring essential metabolites in the body and usually have a similar chemical structure.

These essential metabolites are generally found in larger amounts in tumor cells and in the rapidly dividing cells of the body.

Polyfunctional Alkylating Agents

The polyfunctional alkylating agents are also called radiomimetic agents, since they act on the cell in the same fashion as does radiation. They comprise a wide variety of chemical structures. Radiomimetic agents alkylate a carboxyl (COOH) group in living material and cross-link DNA, thereby producing gene mutation, chromosomal damage, and an inability of the cell to reproduce.

Antitumor Antibiotics

The antitumor antibiotics are substances isolated from soil microorganisms. For the most part, these drugs are not employed in the common bacterial diseases of man but only for certain tumors.

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*Presented at the Annual Midsummer Meeting of the International College of Surgeons.

†Professor of Surgery, New York Medical College.

TABLE 1

Antimetabolic Agents of Value in the Treatment of Disseminated Neoplastic Disease in Humans

I. Folic Acid Antagonists
   A. Aminopterin
   B. Methotrexate (MTX)

II. Purine Antagonist
   A. 6-Mercaptopurine (Purinethol) (6MP)
   B. Azathioprine (Imuran)

III. Pyrimidine Antagonist
   A. 5-Fluorouracil (5FU)
   B. 5-Flouro-2′-Deoxyuridine (FUDR)
   C. 5-Iodo-2-Deoxyuridine (IUDR)
   D. 6-Azauridine (AzUR)

TABLE 2

Polyfunctional Alkylating Agents of Temporary Value in the Control of Human Neoplastic Diseases

1. Nitrogen Mustard (Mustargen) (HN_2)
2. Ethyleneimines
   Tri-Ethylene Melamine (TEM)
   Triethylene-Thiophosphoramide (THIO-TEPA)
   Thiadiazolephosphoramide (Azatepa)
3. Chlorambucil (Leukeran)
4. Nitrogen Mustard-N-Oxide (Nitromin)
5. Mannitol Mustard (Degranol, BCM)
6. Cyclophosphamide (Endoxan, Cytoxan)
7. Uracil Mustard
8. Busulfan (Myleran)
9. Phenylalanine Mustards
   Sarcolysin (DL Form)
   Melphalan (L Form)

TABLE 3

Antitumor Antibiotics Useful in the Treatment of Cancer in Man

1. Actinomycins C & D
2. Mitomycin C
3. Mithramycin (PA144)
4. Streptonigrin

Enzymes

Enzymes are proteins secreted by the body cells that act as catalysts inducing chemical changes in other substances, themselves remaining apparently unchanged in the process.

Others

The *miscellaneous agents* are compounds whose mechanisms of action are unknown. The steroids are compounds. *Tables 1, 2, 3, 4, 5, and 6* show the names of the useful drugs. *Table 7 shows* the tumor types, the drugs which have been demonstrated to be effective and the percentage of anticipated response.

These results are derived both from our study of 1900 patients with advanced cancers of various types at New York University Medical Center and from the studies of Dr. Sidney Farber at the Children's Cancer Research Center in Boston. Today there are a group of tumors very sensitive to the effects of one or more of the cancer chemotherapeutic agents, and also a group quite resistant to the drugs presently available.

Clinical Uses

Choriocarcinoma

The most impressive results with the use of the anticancer chemicals are seen in the treatment of women with choriocarcinoma: tumors arising from the placenta. Of women with these tumors, including those in advanced stages of disease, approximately 75 percent can be cured, with complete disappearance of the tumor, for periods up to five to 15 years with the use of the metabolic antagonists—Methotrexate, 6 MP, and the antibiotic Actinomycin D. For this reason, chemotherapy has become the modality of choice in this group, rather than surgery or radiation therapy.

In some young men with the advanced embryonal cell or choriocarcinoma of the testes treated with several drugs — Mithramycin, Actinomycin D, Methotrexate, Velban, and Leukeran, the disease has completely disappeared for up to seven or eight years. While surgery and radiation therapy are the treat-

ments of choice in the early stages, chemotherapy is employed in those cases not cured by these modalities.

Lymphoblastomas

The next group of tumors very sensitive to the action of a variety of the anticancer chemicals are the acute and chronic leukemias, the lymphosarcomas, and Hodgkin's disease. The large majority of these tumors respond with partial or complete disappearance of all the disease with the use of the polyfunctional alkylating agents, alkaloids from the periwinkle plant, namely Velban and Vincristine, with Methotrexate and with the Methylhydrazine L.Asparaginase, the antitumor antibiotics, the hormones, cortisones, and ACTH. The duration of complete good health in some of these patients has now been up to 18 years with the use of drugs alone. Similar results are obtained with the use of radiation therapy. In the acute leukemia of children, however, drugs are the therapy of choice: given singly or in a wide variety of combinations. There are now in the United States some 200 children with leukemia, free of their disease for five to 15 years following the use of drugs.

Wilms's Tumor

In children with Wilms's tumor of the kidney, some 80% respond to treatment with Actinomycin D, radiation therapy and surgery. In some advanced cases this therapy has led to complete disappearance of the disease for over five years.

Malignant Melanoma

For an occasional patient with a malignant melanoma arising from a black mole localized to an extremity, the administration of the phenylalanine mustard or Actinomycin D by the regional perfusion technic has provided complete tumor disappearance for many years. If the disease is disseminated over the entire body only temporary palliation is possible for a short period of time.

Breast Carcinoma

In the common advanced carcinoma of the breast in women, radiation therapy, hormone

TABLE 4

Miscellaneous Drugs Useful in the Treatment of Cancer in Man

1. Urethane – (Ethylcarbamate)
2. The Vinca Alkaloids
   - Vinblastine Sulfate (Velban) (VLB)
   - Vincristine
3. Colchicine Derivatives
   - Demecolcin
   - Trimethylcolchicinic Acid Methyl Ether D–tartrate (TMCA)
4. O, P'DDD (1, 1-Dichloro-2-(O-Chlorophenyl) –2–(P-Chlorophenyl) –Ethane)
5. Quinacrine (Atabrine)
6. Methyl Gag (Methylglyoxal-BIS(Guanylhydrazone)
7. Methyl-Hydrazine (Natulan)

TABLE 5

Enzymes of Use in Advanced Neoplastic Disease

1. L-Asparaginase

TABLE 6

Hormones and Ablative Therapy of Some Temporary Value in Human Neoplastic Disease

1. ACTH, Cortisone and Analogues
2. Androgens
3. Estrogens
4. Dihydroxyprogesterone (Delalutin)
5. Ablative Therapy
   - Oophorectomy
   - Orchiectomy
   - Adrenalectomy
   - Hypophysectomy

TABLE 7
Tumor Responses to Chemotherapy

Primary Site or Cell	Drugs Used	% Response
Adrenal	O,PDDD	30%
Bladder	Thiotepa, Cyclophosphamide, Fluorouracil	10%
Brain	Mithramycin	15%
Breast	Androgens, Estrogens, Steroids, Fluorouracil, Alkylating Agents, Methotrexate, Vinca-Alkaloids	20%
Cervix	Vincristine, Methotrexate	10%
Colon-Rectum	Fluorouracil	20%
Endometrium	Progesterens	30%
Hodgkin's Disease	Alkylating Agents, Vinca Alkyloids, Methyl-Hydrazine, Steroids	80-90%
Head & Neck	Methotrexate, Fluorouracil, Alkylating Agents	20%
Kidney (Adeno)	Testosterone	10%
Wilms's Tumor	Actinomycin D*, Vincristine	80% 40%
Liver	5-Fluorouracil	10%
Lung (Epidermoid)	Alkylating Agents	10%
Lung (Oat Cell)	Alkylating Agents	30%
Acute Leukemia Children	Methotrexate, 6-Mercaptopurine, Vincristine, Cyclophosphamide, Steroids	80-90%
Chronic Lymphatic Leukemia	Alkylating Agents, Steroids	50%
Chronic Myelocytic Leukemia	Alkylating Agents	90%
Lymphosarcoma	Alkylating Agents, Vinca Alkyloids and Steroids	50%
Melanoma	Alkylating Agents, Imadizole Carboxymide	10%
Myeloma	Alkylating Agents, Urethan	30%
Ovary	Alkylating Agents, Fluorouracil	30-40%
Pancreas	Fluorouracil	10%
Placenta (Chorio)	Actinomycin D, Methotrexate	75%
Prostate	Estrogens	60%
Sarcoma (Adults)	Vincristine	10%
Stomach	Fluorouracil, Mitomycin C	10%
Testis Seminoma	Alkylating Agents	40%
Testis Embryonal	Mithramycin, Actinomycin D	40%

*Used with Radiation Therapy.

therapy, the eradication of some hormone-producing glands and the wide variety of anticancer drugs can play an important role in the palliation of the disease for several years, though cures have not yet been obtained. Patients who improve live not only twice as long as those who do not respond, but they live longer more comfortably. In early carcinoma of the breast in women, there is an over-80%, five-year cure today with the use of surgery and/or radiation therapy. With mammographs and other newer diagnostic techniques to detect the disease at an earlier stage, hopefully a higher percentage of cure will be seen.

Prostate Carcinoma

Cancer of the prostate can be controlled for years with the use of estrogens and orchiectomy.

Ovarian Carcinoma

Another tumor moderately sensitive to chemotherapy is carcinoma arising in the ovary. Approximately 50% of women can be significantly palliated for months to years with the use of one of the following metabolic antagonists: the polyfunctional alkylating agents, Velban, Fluorouracil and radiation therapy.

Gastrointestinal Tract Carcinoma

The common adenocarcinomas of the gastrointestinal tract, stomach, pancreas, large bowel, and rectum, are moderately sensitive to therapy with the antagonist Fluorouracil or the antibiotic Mitomycin C. Roughly one third of these patients can experience partial disappearance of their tumor masses and of pain, and even gain weight. This improvement lasts on the average eight months, but may continue from one to two years.

Other Tumors

Similarly with squamous cell tumors arising in the head and neck area, control of the disease may occur with the use of Fluorouracil or Methotrexate.

Tumors which have been resistant to all forms of chemotherapy employed to date are the primary malignant tumors of the bone and cartilage and of the fat, and also some of the other soft tissue sarcomas.

Conclusion

In conclusion, chemotherapy is now established as another modality in the care of the patient with cancer. Hopefully, as new drugs appear, further control will be possible.

Centenarians

Substance, Not Shadow

If this were the only prospect looming on the far horizon of human life, men and women would fervently pray that they might quit this world of tribulation before the evil days came. But the ideal of old age which they cherish is something very different. They wish a green old age, but a green old age with the power to enjoy still undiminished. Longevity connotes for such not benumbing senility, but full-blooded existence, a life which till the last dread hour shall be lived in tolerable possession of physical and mental faculties. In fine, they crave the substance, not the shadow.*

*W. Forbes Gray: Five Score, 1931.

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Humanities

The Physician in Spite of Himself—Moliere*

Thibaut: Sir, we come to look for you, my son Perrin and myself.

Sganarelle: What is the matter?

Thibaut: His poor mother, whose name is Perrette, has been on a bed of sickness for the last six months.

Sganarelle: (Holding out his hand as if to receive money) What would you have me do to her?

Thibaut: I would like you to give me some little doctor's stuff to cure her.

Sganarelle: We must first see what is the matter with her.

Thibaut: She is ill with the hypocrisy, Sir.

Sganarelle: With the hypocrisy?

Thibaut: Yes; I mean she is swollen everywhere. They say that there is a lot of seriosities in her inside, and that her liver, her belly, or her spleen, as you would call it, instead of making blood makes nothing but water. She has, every other day, the quotiguian fever, with lassitude and pains in the muscles of her legs. We can hear in her throat phlegms that are ready to choke her, and she is often taken with syncoles and conversions, so that we think she is going off the hooks. We have got in our village an apothecary—with respect be it said—who has given her, I do not know how much stuff. But all this, as people say, was nothing but an ointment of fiddle-faddle. He wanted to give her a certain drug called ametile wine; but I was downright afeard that this would send her to the other world altogether; because they tell me that those big physicians kill, I do not know how many, with that new-fangled notion.

Sganarelle: (Still holding out his hand, and moving it about to show that he wants money) Let us come to the point, friend, let us come to the point.

Thibaut: The point is, Sir, that we have come to beg of you to tell us what we must do.

Sganarelle: I do not understand you at all.

Perrin: My mother is ill, Sir, and here are two crowns which we have brought you to give us some stuff.

Sganarelle: Ah! *you* I do understand. *There* is a lad who speaks clearly, and explains himself as he should. You say that your mother is ill with dropsy; that she is swollen all over her body; that she has a fever, with pains in the legs; that she sometimes is taken with syncopes and convulsions, that is to say with fainting fits.

Perrin: Indeed Sir! that is just it.

Sganarelle: I understand you at once. Your father does not know what he says. And now you ask me for a remedy?

Perrin: Yes, Sir.

Sganarelle: A remedy to cure her?

Perrin: That is just what I mean.

Sganarelle: Take this then. It is a piece of cheese which you must make her take.

Perrin: A piece of cheese, Sir?

Sganarelle: Yes; it is a kind of prepared cheese, in which there is gold, coral, and pearls, and a great many other precious things.

Perrin: I am very much obliged to you, Sir, and I shall go and make her take it directly.

Sganarelle: Go, and if she dies, do not fail to bury her in the best style you can.

Editor's Note: Dr. Sganarelle seemed like a mercenary fellow but he probably was a good psychologist and knew that unpaid advice is usually not heeded.

*Seventeenth Century.

Radioisotopes

Changing Concepts in Therapy

RITA F. GIROLAMO, M.D.*
Paterson, New Jersey

THE TITLE OF CHANGING concepts in therapy relating to radioisotopes is inappropriate since there have been no changes in the concept of radiation therapy in the past 70 years. Since the discovery of x-ray by Roentgen in 1896 the main principle of radiation therapy, namely to administer radiation homogeneously throughout the area of interest, has not changed one iota. The use of radioisotopes in radiation therapy is also long-standing. It relates to the early 1900s when radium, which is a radioisotope, was first used therapeutically. For many years radium has been the mainstay of the armamentarium of the radiation therapist.

Radioactive Materials

Radium

Radium in itself is not the radioactive metal which is used for therapeutic purposes. By means of nuclear disintegration an alpha particle is emitted which produces radon which, after successive emissions of additional alpha particles, forms radium B, C, D, E and F. It is radium B and C that are the solids which emit gamma rays for therapy. Radium is utilized in many modalities, including teletherapy, surface applications, interstitial and intracavitary uses.

Artificial Radioactivity

The discovery of artificial radioactivity has introduced two new modalities of application of radioactive materials: internal and intracavitary. Rutherford first discovered artificial radioactivity in 1919. In 1932 Lawrence was able to produce a small amount of radioactive material in the cyclotron, and in 1938 he introduced the first successful use of artificially produced radioactive material, ^{32}phosphorus for the treatment of leukemia.

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Radionuclides

The application of radionuclides for effective radiation therapy follows the same guidelines as radium and x-ray therapy. The cobalt 60 bomb has effectively replaced the radium bomb and conventional orthovoltage x-ray generators. Numerous artificially produced radioisotopes have replaced radium in all its modalities of application. The availability of radionuclides to be administered parenterally and intracavitarally in solutions has offered many advantages over the previously limited applications of both radium and x-ray radiation. Selective localization of the administered radioisotopes within the tumor produces the ideal situation that the therapist is constantly seeking. The resultant effect is to have a localized radiation-producing unit within a tumor without the usual accompanying radiation to normal tissue. This type of radioisotope should have a short biologic half-life and a radiation spectrum which will give efficient therapy. One of the major pitfalls in this ideal situation is the inability to develop radioisotopes which will be accumulated in sufficient concentration to be effective therapeutically. It is extremely simple to obtain adequate localization for diagnostic radioisotopic techniques. To attempt to overcome this deficiency, many devices have been contrived in an attempt to deliver the radioisotopes to the proper area. Many new isotopes have been developed in the past 10 years; some have been replaced, and new applications have been found for old ones (Table 1).

Use of Radionuclides

The internal use of radionuclides has been somewhat disappointing. These radioisotopes can be administered either orally or parenterally in organic forms.

^{131}Iodine

^{131}Iodine has an excellent accumulation within the thyroid gland and affords many applications in diagnostic problems. Its localization, however, within thyroid carcinoma is extremely erratic and therefore not suitable to deliver uniform radiation. Only follicular types of carcinomas consistently localize radioactivity.

^{32}Phosphate

^{32}Phosphate, as a soluble salt, has been successfully used intravenously as the treatment of choice for polycythemia vera. Good response is usually obtained in chronic leukemia and for palliation of bone metastases. In order to increase the selective localization of radioactive phosphorus within the bone metastases Tong and Rubinfeld[1] have developed an enhancement technique; parathyroid hormone is administered intravenously and, after cessation of parathyroid, ^{32}phosphate is injected, taking advantage of the rebound phenomenon.

^{125}Iodine

^{125}Iodine has been tagged to chloraquine and other analogues for experimental treatment of melanomas. Its localization diagnostically in melanotic melanomas has been documented for many years, and this therapeutic application holds some promise. Radioisotopes are used internally in non-soluble

TABLE 1
Radioisotopes in Therapy

Radioisotope		Use
^{131}I	Sodium iodide	Thyroid cancer
^{32}P	Sodium phosphate	Polycythemia vera Chronic leukemia Metastatic bone cancer
^{32}P	Colloidal chromic phosphate	Treatment of peritoneal effusions Treatment of pleural effusions
^{198}Au	Colloidal gold	Treatment of peritoneal effusions Treatment of pleural effusions
^{198}Au	Gold seeds or wires	Interstitial implants into tumors
^{60}Co	Cobalt needles or wires	Interstitial implants into tumors
^{60}Co	Cobalt teletherapy	External radiation of tumors
^{90}Sr	Strontium applicator	Treatment of eye lesions
^{192}Ir	Iridium seeds	Interstitial implants into tumors
^{182}Ta	Tantalum wires	Interstitial implants into tumors
^{90}Y	Yttrium seeds or microspheres	Interstitial implants into tumors

forms such as radiocolloids, but their use has been limited due to the inconsistent clearing of these nuclides by the liver, spleen and bone marrow.

^{206}Bismuth

Recent work has been reported on suspensions of larger particles absorped on carbon, especially ^{206}bismuth. The development of ceramic microspheres, which are particles ranging from 10 to 200 microns, has provided many useful therapeutic applications. These microspheres tagged with various radionuclides localize activity within the vascular bed of the tumor by actually causing microemboli. They must of course be delivered to the tumor site either by selective intra-arterial catheterization or isolation perfusion techniques. They offer a distinct advantage over perfusion techniques with chemotherapy since there is no passage of the radionuclides into systemic circulation to cause any radiation effect such as bone marrow depression.

Radioactive Colloids

Suspensions of radioactive colloid have been used intraperitoneally and intrapleurally for treatment of lymphatic effusions. ^{198}gold, ^{32}phosphorus and ^{90}yttrium have been used; however, the pure beta emitters such as phosphorus and yttrium are preferable due to their absence of gamma radiation which produces radiation detection problems. At our institution radioactive colloids are reserved for cases where chemotherapeutic agents have failed. There are several series being studied on prophylactic radiocolloids postoperatively where no gross evidence of peritoneal or pleural metastases is detectable.

Use of Radium

Aside from these two new modalities of administering radiation to patients, the remainder are merely substitutes for the time-tested uses of radium (Figure 2). One may wonder why there should be an attempt to supplant radium therapy. When one reviews the physical properties of this nuclide it becomes apparent that, although it is therapeutically efficient, it is undesirable from a radiation safety viewpoint.

TABLE 2
Other Radioisotope Substitutes for Radium

	T ½	Gamma energy in mev	Half-value layer (hvl) in cm. Pb
^{226}Radium	1620y	01.05 – 2.4	1.2
^{60}Cobalt	5.2y	1.17, 1.33	1.2
^{222}Radon	3.8d	0.2 – 2.2	
^{182}Tantalum	115d	1.12 – 1.22	
^{137}Cesium	30y	0.66	0.5
^{198}Gold	2.69d	0.411	0.3
^{192}Iridium	74d	0.3 – 0.6	0.3

The Permanence of Radium

The major advantages of radium are the permanence of the sources, since the half-life of ^{226}radium is 1600 years. These sources therefore never need calibration; they are always available; they are inexpensive, and they have been utilized for so many decades that their techniques and distribution patterns have been very well documented. The gamma ray energy, however, is up to 2.4/mev, which means that the radiation hazard to personnel is a serious problem. With such high energy radiation, protection by means of lead is impractical since it is impossible to wear a lead apron 1.2 cm. thick. This is called the half-value layer of radium, which means the thickness of lead absorber necessary to cut down the radiation from radium to one half. It is quite obvious that wearing a lead apron in an operating room for the insertion of intracavitary radium is worthless from a safety viewpoint and also unnecessarily cumbersome. The best protection against radiation is the shortest exposure time. In order to obviate this problem after-loading applicators have been developed, for example, the Fletcher cervical applicator. This applicator is inserted into the cervix and uterus in the operating room and, after localizing x-ray films are obtained and the applicator is in satisfactory position, the radium is loaded into the patient. This minimizes the radiation exposure to the professional, technical and nursing staff. There are two other problems, however. One is the rigid construction of the needles and the tubes which makes it extremely difficult to implant them in a uniform pattern

or in a tumor which is not easily accessible. Second is the problem of breakage with subsequent leakage of alpha radiation which is extremely injurious to the lungs.

Radium Substitutes

The ^{60}*cobalt* and ^{182}*tantalum* have obviated one of the minor disadvantages of radium, namely rigidity. They can be made into flexible wires or nylon ribbons for interstitial implantation of accessible tumors. Due to the high gamma ray spectrum which ranges up to 1.3 mev, radiation hazard still remains a problem. ^{192}*Iridium,* however, overcomes both of the major disadvantages of radium. The soft gamma radiation averages 400 Kev. The unit is 1000 electron volts compared to the million-electron volt of radium. It can also be incorporated into flexible wire seeds for easy interstitital applicators.

^{137}*Cesium* can be substituted for radium where rigid needles and applicators can be used; however, it has an energy spectrum of only half that of radium. The half-life is also long, 33 years, so that calibration is not needed frequently. ^{198}*Gold seeds* have replaced the use of radon seeds; they have the advantage of being metallic seeds rather than seeds containing gaseous radon. The gamma energy is one quarter that of radon, a definite improvement in radiation exposure. Radioisotopes have been developed that decay by electron capture which results in the emission of a low-energy characteristic x-ray. In 1958 Harper indicated the possible clinical applications of ^{131}cesium and ^{103}platinum, both of which are in the 30 Kev range.

A very commonly employed sealed-source substitute for radium is ^{90}*yttrium:* the daughter nuclide of the ^{90}*strontium-*^{90}*yttrium* series. Both of these isotopes are pure beta emitters of high energy and have been used as surface applicators or as interstitial implants. The use of a ^{90}*strontium* eye applicator is undoubtedly familiar to all of you and has certainly replaced the use of radium molds. ^{90}*Yttrium* can be incorporated into pellet seeds or microspheres as a permanent implant since its half-life is 2.67 days. It has been used very effectively and dramatically in radiation hypophysectomy for carcinoma of the breast and prostate, using either transcranial or transnasal approaches. Harper in 1964 developed a very ingenious strontium-yttrium needle at the Argonne Cancer Institute. The ^{90}*strontium* source which is located on the end of a stainless steel needle provides a continuous supply of high-energy beta and has been used very simply for radiation hypophysectomy and very successfully in percutaneous chordotomies for intractable pain.

Radiocolloid or ^{131}*iodine*-tagged oily contrast material such as ethiodol has been injected intralymphatically to treat retroperitoneal and other lymph nodes. As localization, however, has been spotty within metastatic lymph nodes, the primary requisite of uniform distribution of radiation is not always achieved. Investigative work is being conducted on the prophylactic use of these intralymphatic nuclides to destroy micrometatases.

As you will note, there are many ingenious attempts at achieving the ideal situation of selective localization of radioactivity within the tumor while sparing surrounding tissue. If one is fortunate enough to have a nuclear reactor it is possible to inject a stable element such as ^{10}*boron,* which is concentrated within some neural tumors. After the tumor with ^{10}*boron* becomes radioactive, alpha particles are produced at the local tumor site.[2]

The rapid progress that is being made in the development of radiochemistry and radiopharmaceuticals gives much hope for effective radiation therapy with radioisotopes.

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2. Farr, L. E., et al.: Neutron Capture Therapy with Boron in Treatment of Glioblastoma Multiforme. Amer J Roentgen 71:279, 1954.

A man's life purpose should be sought out, thought out and wrought out.
—Earl of Oxford.

Angiography and Endoscopy

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THE DEVELOPMENT and perfection of fiberoptics have revolutionized the field of gastrointestinal endoscopy. The concept of the transmission of images by means of a bundle of transparent fibers was patented in 1928 by Baird of England. However, it was not until 1954, 16 years ago, that fiberoptic systems became practical. At that time it became possible to coat individual fibers with material of a lower refractive index which minimized light loss and increased image resolution. In 1957 the first ACMI scope was produced, whereby the image is transmitted by a fiber bundle consisting of 150,000 glass fibers, 11 microns in diameter.

The Fiberoptic Scope

It was not until 1963 that Hirschowitz reported the development of a fiberoptic esophagoscope which incorporated straight-ahead viewing, a fiber-light source, and channels for air suction and biopsy. In addition to the obvious advantages of patient comfort and safety when compared with rigid esophagoscopes, fiber esophagoscopes permit the observation of peristalsis. Modifications of the gastroscope and esophagoscope enable us not only to visualize a lesion but also to photograph it, biopsy it, and obtain washings for cytological diagnosis. This, in conjunction with radiology, enables us to differentiate correctly between benign and malignant ulcers in 97% of the cases. If the lesion is frankly malignant, we can avoid the delay of conservative medical management by recommending immediate surgery. In many cases we are also able to tell our surgical colleagues the extent of the lesion, and this knowledge may influence or even alter their choice of a particular operative procedure.

Our procedures are done under local anesthesia; thus the risks of general anesthesia are avoided. With flexible endoscopes there are

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practically no absolute contraindications to endoscopy, except an uncooperative patient. We feel that every gastric ulcer should be scoped to ascertain whether it is truly benign and not malignant.

All patients with x-ray evidence of esophageal lesions should be scoped. In addition, biopsy should be done if feasible to help establish a tissue diagnosis.

Angiography

In the field of angiography great strides have been made in the past fifteen years; the procedure is now applicable in all age groups, including infants and children. The technique is simple: percutaneous puncture.

Selective Catheterization

The equipment needed includes an image intensifier with television monitoring of the catheter tip which is then maneuvered into an appropriate branch of the aorta. This is known as "selective catheterization." Selective catheterization has certain advantages over aorta injections: 1, it helps us avoid overlap of other aortic branches; 2, a larger dose of contrast media can safely be given to individual viscera with the exclusion of the kidneys, thus giving better opacification and visualization.

Contraindications

Contraindications to a selective angiography are few, the only absolute contraindication being a previous anaphylactic reaction to injection of the contrast medium. Relative contraindications include: 1, low cardiac output; 2, anuria; 3, allergy to iodinated agents; 4, bleeding tendencies; 5, absence of a pulse distal to the proposed puncture site; 6, local infection at the proposed site; 7, evidence of cholesterol emboli in the fundus.

Complications

Since new dyes have been introduced there are practically no complications; mortality rate now is 0.06 percent. The serious complications have been reported as high as 1.9 percent, but a recent study has reduced this to 0.5 percent. The complications most feared are thrombosis and embolization.

Indications

Arteriography is indicated in cases where the hepatic scan either has shown a lesion or is equivocal.

Angiography of the liver is best accomplished by selective injection of either the hepatic artery or the portal vein, because the entire hepatic parenchyma is opacified in this manner. Of the two, hepatic artery injection is probably the better since: 1, it is less hazardous and easier to perform; and 2, most neoplasms derive their blood from the hepatic artery and not from the portal vein.

Clinical Application

The advantages to the operating surgeon are obvious. Angiography of the liver tells the surgeon about the type of mass, its anatomic location and its relation to the hepatic arteries. *The accuracy rate of diagnosing lesions of the liver approaches 70 percent.* This compares favorably with a diagnostic accuracy rate of liver biopsy which is about 70 percent, the same as for hepatic scan. Of course angiography is not a screening procedure; the screening procedure is that of hepatic scanning. If the hepatic scan is equivocal or positive and surgery is contemplated, then angiography is indicated.

When it comes to angiography of *the pancreas,* the unanimity of opinion disappears. The major problem is the variable vascular anatomy of the pancreas. The pancreatic artery has multiple sites of origin; therefore we must catheterize the hepatic, splenic and superior mesenteric selectively, plus branches of the pancreatic artery. Often this is not technically feasible. It is also time-consuming. Tumor neovascularization is frequently lacking in pancreatic carcinoma. Tumor vessels and stain are difficult to recognize, and vessel displacement is not constant. Nevertheless, some studies purport to show that 60 to 80 percent of pancreatic carcinoma will show angiographic changes with an incidence of about 10 percent of false positive. We are talking here about a disease that has shown an increase of 12 percent in men and 22 percent in women in the

past 21 years. Thus we need all the help we can get.

To summarize: angiography and endoscopy remain two valuable clinical tools in diagnosing a gastrointestinal malignancy: tools that can greatly assist the surgeon prior to a definitive operative procedure.

Abstracts

Direct Myocardial Revascularization with Saphenous Vien Autograft

This paper reviews the first 100 operations for direct anastomotic reconstruction of the arterial system performed at the Cleveland Clinic. These represent cases both of excision and graft and aortal coronary artery anastomosis; 41 were also accompanied by unilateral or bilateral internal mammary implants. There were five hospital deaths and three late deaths at the time of this publication. There were 36 non-fatal complications, all of which were controlled with medical regimen, and each patient recovered fully. In 50 patients postoperative arteriography was performed, revealing the graft to be patent in 39, slightly narrowed in one, narrowed 50 percent in six and occluded in four. Numerous reproductions of excellent coronary arteriograms accompanied this article.

Sheldon, M.D., F.C.C.P., and Mohammed Riashi, MD. Dis Chest 56:4:279, 1969

Pneumomediastinum

This article reports four cases of pneumomediastinum seen within a nine-month period in one hospital. Various signs and symptoms are reviewed. Excellent x-rays accompany the monograph, and the benign nature of this disease is emphasized.

Theodore A. Peterson, M.D.
Minneapolis, Minnesota

Charles E. Millard, M.D. Dis Chest 56:4:297, 1969.

One Man

It has been aptly said that any successful institution is the length and the shadow of one man. Nobody ever heard of *a journal* that made its mark from the inspiration of a committee or a board of directors. Behind each one, giving its vigor, its personality, its force for good or ill, has been a single man.

Vermont Royster Pride and Prejudice

Freedom

Freedom is the air you breathe and the sweat you sweat. It is you, and a hundred and sixty million people like you, with your chins up daring anybody to take it away from you.—Origin Unknown.

Who Follow a Gleam

Leopold Auenbrugger

"It seethes like boiling vinegar; it creaks like a new leather strap." Thus did the Hippocratic School describe the sinister sounds spontaneously emitted by diseased chests, the portentousness of which was to remain a mystery for over a thousand years until a physician-in-chief at Holy Trinity Hospital in Vienna became too impatient to continue practice under the shadow of ignorance and despair then prevailing about chest diseases.

That doctor was Leopold Auenbrugger (1722-1809). In the diseased chests of cadavers he autopsied he frequently found water and wondered why such lethal fluid could not have been detected before death and drained off. That was what puzzled Auenbrugger. His assistant, Hans, could give him no encouragement: how, he asked his master, could you find out what was in the chest cavity when it is inaccessible to touch and invisible to sight within its bony armor?

All too true, admitted Auenbrugger, but there must be a way! Suddenly, one fine day, the clouds auspiciously broke. Why not thump the chest and listen?

"When I was a boy," he eagerly related to Hans, "I used to have to serve the wine in my father's inn at Graz. Often my father sent me to the cellar to tap the wine casks to see how much of each kind of wine was left. Above the level of the wine, you see, was always air. If I struck below the wine level, the tone was high and flat. And if I struck the cask above the wine level, the sound was musical and low.

But Hans was puzzled. What had wine casks to do with human chests?

"Don't you see," explained Auenbrugger, "if a chest has a certain sound when it is full of air—when it is normal and healthy—that sound is sure to be different if the chest has water in it.

But Hans remained confused and dubious.

Whereupon to prove his point, Auenbrugger thumped the fluid-filled chest of a cadaver and then both his own healthy chest and the bewildered Hans's. Triumphantly he pointed out the difference in sound.

Thereafter, for seven years Auenbrugger followed his gleam. He thumped patients' chests industriously, listened intently and, by comparing the resonances, became adept at correlating them with thoracic health or morbidity. When the sound his thumping elicited indicated fluid in the chest cavity, he drained it off, thereby appreciably reducing the previously soaring mortality incidence.

Then he wrote a book on the subject of percussion: "The New Invention, Which Enables the Physician from the Percussion of the Human Chest to Detect the Diseases Hidden Within," which stated in part:

The duller the sound, and the more nearly approaching that of a fleshy limb stricken, the more severe the disease.

The want of the natural sound behind indicates more danger than it does on the anterior and superior part of the chest.

The total destitution of sound over one whole side is generally a fatal sign.

Was Auenbrugger honored for his extraordinary feat of medical induction? No! His revolutionary theory of percussion was ignored until Napoleon's doctor, Corvisart, became enamored of it, employed it in his practice, thereby popularizing and conserving the procedure to be later refined into stethoscopic auscultation by Rene Laennec following the same gleam as had beckoned Leopold Auenbrugger.

With acknowledgements to E. R. Montgomery: The Story Behind Great Medical Discoveries; H. S. Glasscheib: The March of Medicine; Brian Inglis: A History of Medicine.

Septic Shock*

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Septic or endotoxic shock is an exceedingly lethal condition which, if not adequately and promptly treated, will result in the death of at least two thirds of the patients affected. Sepsis is surpassed in frequency only by hemorrhage and myocardial infarction as a cause of clinical shock. Any surgeon, in any specialty, may encounter this problem at some time in his career and, when it happens, events precipitate themselves with dramatic rapidity. There is not much time for study or discussion; it is, therefore, imperative to be able to recognize the earliest symptoms, and even the situations that may lead to septic shock, so that immediate steps can be taken to forestall a lethal outcome.

Etiology

Bacterial Toxin

Although the pathophysiology of endotoxic shock is not yet completely understood, the vascular collapse resulting from sepsis is thought to be caused by the presence of an overwhelming amount of bacterial toxin in the circulation, causing drastic vasomotor effects. *Gram-negative bacteria* are the most common offending organisms, but endotoxic shock may also occur with gram-positive bacteria and, occasionally, with viruses, fungi, and rickettsiae. A common etiological factor in the production of septic shock is an infected pregnancy, especially an abortion, and the terrifying aspects of gram-negative septicemia are feared by all obstetricians.

Infected Abortion

The typical candidate for endotoxic shock is a patient with a late infected abortion, usually over ten to twelve weeks of gestation, who is admitted to the hospital with a temperature of 103°F. or more, only slight blood loss, minimal pelvic and abdominal tenderness, and perhaps a

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history of having received a chemical douche. There is usually a serous or seropurulent vaginal discharge.

Treatment

Although a positive blood culture provides the ultimate proof of bacteremia and identifies the organisms involved, such evidence can only be obtained in less than half the cases, and treatment must usually be initiated and carried out without positive bacterial identification.

Massive Therapy

Treatment involves control of the existing infection by massive antibiotic therapy, maintenance of effective circulation by restoration of adequate volume and the judicious use of corticosteroids and vasoactive drugs, and, most importantly, the eradication of the focus of infection.

Evacuation of Uterus

If an infected abortion is evident, this means evacuation of the uterus as soon as possible; this should not be delayed more than absolutely necessary and should be carried out even if the patient has not become afebrile. Hysterectomy should be considered early if the patient is found to be unresponsive to curettage.

Control of Venous Pressure

One of the most important advances in the management of patients in septic shock or impending shock is the monitoring of the central venous pressure as a routine procedure. It is the best guide to intravenous fluid therapy by reflecting the ability of the heart to handle the circulating blood volume.

Monitoring the urinary output is, of course, an integral and essential part of the management of shock of any kind.

As in all fields of medicine, prevention is better than cure: early recognition and prompt and vigorous therapy of the potential case will often forestall the development of the shock state. Amnionitis and postpartum endometritis must be vigorously treated. Contamination of the urinary tract should be carefully avoided and promptly treated if it occurs, as urinary tract infection is the leading cause of bacterial shock. Pelvic and abdominal abscesses should be adequately managed by indicated surgery and antibiotic therapy.

Christopher J. Allan, M.D.

The cover photograph was taken on a trip Dr. Allan made to Eastern Canada between graduation from medical school and the beginning of his internship. He and his wife were driving along the coast in New Brunswick and kept passing scenic coves such as the one in the photograph. Each time they got just beyond the point of stopping, his wife or he would remark that "they should have taken a picture." So they decided that they would stop at the very next scenic spot and take a picture; the result of that stop is the picture of the cove and lobster traps. The lighting characteristics were provided by a sunset behind Dr. Allan when the picture was taken.

Dr. Allan is presently a third-year resident in pathology at the Mayo Clinic.

Security

It is common talk that every individual is entitled to economic security. The only animals and birds I know that have economic security are those that have become domesticated—and the economic security they have is controlled by the barbed-wire fence, the butcher's knife and the desires of others.

They are milked, egged, skinned, or eaten up by their protectors.

Ray Lyman Wilbur.

Septic Shock

Management of Intra-abdominal Abscesses*

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A DEFINITION of shock is difficult. It has been equated with: 1, weakness, coolness, sweating, clouding of the sensorium, or 2, peripheral vascular collapse, or 3, sudden fall in blood pressure. Interestingly enough, *none* of these needs to be present. Shock may be more practically defined as an *acute circulatory deficiency*—central or peripheral—with *inadequate blood flow* to the major organs. The sequence of events usually comprises hypovolemia, perfusion deficit, hypoxia, and metabolic changes.

Especially involved are these organs: 1, the *kidneys*—with activation of the renin-angiotensin and aldosterone systems; 2, the *intestines*—with liberation of toxins and bacteria; 3, the *liver* and other parts of the reticuloendothelial system—with loss of detoxification capacity; 4, the *respiratory* and *hematologic* systems—with upset of buffering and clotting mechanisms.

Bacteriology

Septic shock is caused by bacteria; gram-negative organisms are responsible in over two thirds of the cases. Most important are: *E. coli, Pseudomonas, Aerobacter, Proteus, Bacteroides,* and *Serratia.* Also significant are *Salmonella* and *Clostridia.* Additionally, one should specifically look for non-clostridial anaerobic and microaerophilic bacteria.

Shock may occur in 20 to 30% of all gram-negative bacteremias, and mortality may range from 40 to 90%, the incidence being somewhat lower in the gram-positive infections. The urinary, gastrointestinal, biliary, and genital tracts are the commonest sources of infections.

Shwartzman Phenomenon

The mechanism of action of "gram-negative" shock or sepsis may be the setting up of a

*Presented at the International College of Surgeons Midsummer Meeting, Lake Placid, New York, July 3, 1969.

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Shwartzman phenomenon. Here is a brief summary of the *Generalized Shwartzman Reaction* (GSR):

If one gives intravenous injections of endotoxin 24 hours apart, there occurs a generalized fibrin deposition and thrombosis in many organs, especially the kidneys, which goes on to acute tubular necrosis, then bilateral cortical necrosis and renal failure. In rabbits, the generalized Shwartzman reaction produces a consumption of coagulation factors (especially II, V, VIII) and platelets, with resultant increased prothrombin time, decreased plasma fibrinogen, and decreased platelets.

Contributing Factors

Only *one* intravenous injection of endotoxin may be required to produce a generalized Shwartzman reaction if (1) there is a blocking of the reticuloendothelial system, or (2) sizable amounts of corticoids have been given, or (3) pregnancy is present (perhaps by release of thromboplastic materials from the placenta, as happens especially in septic abortion).

In the generalized Shwartzman reaction and endotoxic shock, then, there occurs the *defibrination syndrome* or *consumption coagulopathy*. This leads to extensive intravascular coagulation, microangiopathy, and hemolytic anemia. These in turn may result in renal failure, hepatocellular jaundice, pancreatitis, and bleeding phenomena.

Peripheral-vascular Changes

The endotoxins cause peripheral vasodilatation, which at first is associated with increased cardiac output and increased peripheral blood flow. As peripheral vascular pooling occurs, there is decreased venous return, and cardiac output falls. Then, with preferential blood supply going to the brain, heart, and lungs, there is anoxia elsewhere. Peripheral vasoconstriction now sets in, which may produce pulmonary capillary hypertension (pulmonary edema or "shock lung"). Venous return further diminishes, cardiac output falls, and there ensue cellular anoxia, metabolic disruption, and ultimately death. Clinically the onset of septic shock may be signalled by a sudden chill, fever, sweating, oliguria, and hypotension.

Management of Septic Shock

Prevention is best: correct diagnosis and prompt surgery (as D&C or abscess drainage) to remove bacteria and thromboplastic materials.

Early Diagnosis of Shock State: note clinical signs; rule out myocardial infarction, pulmonary embolism, hemorrhage.

Laboratory Studies: do immediate gram stain, take *cultures* before giving antibiotics, check platelets, fibrinogen, split fibrin products, blood pH, electrolytes, PaO_2, $PaCO_2$, BUN, lactate, pyruvate, electrocardiogram.

Antibiotics: start with cephalothin, kanamycin, colistin, until culture sensitivity studies are made.

Fluids: lactated Ringer's, 10% dextrose, dextran, occasionally whole blood; use central venous pressure to gauge blood *flow*, not volume.

Maintain Airway: give oxygen, perhaps use respirator.

Drugs: no levophed or other vasoconstrictors; use isoproterenol, corticoids (500-1000 mg. cortisol equivalent), and perhaps heparin.

Heparin can be very valuable, though it may seem hazardous to give it in the presence of bleeding. However, heparin can *treat* and *prevent* generalized Shwartzman reaction and consumption coagulopathy. It should be given before irreversible renal damage occurs. Some men give 1000 units i.m. q.4.h., some 1000-4000 units i.v.q.4.h. Others advise as much as 1000-2000 units i.v. hourly, or as a continuous infusion. Clotting time is a poor index of heparin dosage control. Better are platelet count, plasma fibrinogen, and split fibrin products (measurable by newer precipitin and immune technics).

Other treatments recommended for septic shock include:

Hyperbaric Oxygen—clinically less effective than in experiments.

Hypothermia—only with uncontrollable fever.

Extracorporeal Perfusion Systems—promising, but unproven.

Epsilon Amino Caproic Acid—inhibits plasminogen activators and fibrinolytic activity of plasmin, and controls formation of split

fibrinolytic products and their anticoagulant effect. However, epsilon amino caproic acid may cause oliguria, hypotension, and a generalized Shwartzman reaction by potentiating intravenous clotting.

Susceptibility to septic shock is greatest in patients who: (1) have undergone surgery or instrumentation of the genitourinary, gastrointestinal, or biliary tracts—especially with open-system urinary catheters, cut-downs, central venous pressure catheters (and even intravenous cardiac pacemakers); (2) are debilitated, by neoplasm, diabetes, cirrhosis, hematologic disorders (e.g., leukemia, agranulocytosis), or burns; (3) have received large doses of antibiotics, steroids, radiation, or immunosuppressive agents.

If these principles are observed, both morbidity and mortality can be greatly reduced.

Image Making

Since America, like Australia, is an open democratic society, almost every spectacular event, important or trivial, is subjected to intensive scrutiny. America is under the searching glare of the world spotlight. Every flaw is noted. Trivial acts tend to be magnified, especially by our own citizens exercising to the fullest their constitutional right of uncensored freedom of speech.

Because the world at large has such high expectations of America, every shortcoming, however small, every failure to come up to expectations is a disappointment—and therefore news. Riots, demonstrations, disasters and protests sell more newspapers than the less spectacular pictures of successful routine and peaceful normality. By way of the headlines last year which would have put American developments in perspective, for example, 99 percent of American youth were not arrested by police, 99 percent of America's youth did not participate in riots and draft card burnings, 99 percent of America's black and white citizens did not loot stores or commit arson or murder but went quietly about their work of building their own lives.

Meanwhile distortions emerge from the emphasis given by our politicians, by radio, TV and the free press. Headlines scream of juvenile delinquency, campus violence, drug addiction, black militancy, dropouts, poverty—in March 1969 the official poverty line was $3,335 a year for a family of four—an income comparable with that of today's skilled European worker—or an income the same as that of a middle-class American a mere generation ago.

Walter L. Rice
American Ambassador to Australia

Editor's Note: We in MINNESOTA MEDICINE *are endeavoring to create the better intellectual image than the distorted one usually portrayed by the unthinking public.*

Life's taxi keeps on marking up the nickels, whether you are driving anywhere or just sitting still.—Cominco Magazine

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It's an appropriate coincidence that the word "American" ends in "I can."—Alexander Animator

The Shape of War to Come

Of the means of waging war biological weapons evoke more than any other sweeping emotions of horror and revulsion. No community has yet had to suffer a large-scale biological attack, but the common experience of the history of all nations has shown what its effects might be.

Not only the insidious qualities of biological weapons and their self-propagating nature within human and animal bodies cause alarm. The lethal doses of these agents are small compared even with chemical weapons. The resistant organism *Coxiella burnetii* which causes the rickettsial disease Q-fever, for example, is considered by chemical and biological warfare experts to be as effective as Sarin in one-millionth of weight by weight quantities of the nerve gas. And biologists with a mathematical bent have calculated that less than one pound of botulinus toxin, a non-contagious toxin of *Clostridium botulinum,* which was being isolated at wartime Camp Detrick, could, in theory at least, kill the whole of the world's population.

An agent which presents itself for such blanket use in these physically small quantities brings it into line for possible use as a strategic weapon. But the qualities of such a weapon which the biological armourer will demand of his biologist are stringent ones if it is to be truly effective. It must be possible to develop the disease-causing pathogenic organism quickly in suitably large quantities in conditions under which it can rapidly reproduce itself without losing its virulence. It must be capable of being stored, again without losing its virulence, for sufficiently long periods so that it can be delivered to its distant target. The war-head or other munition which deposits it on its target must be so devised that the organism is not itself destroyed by the pressurized or other mechanical explosive device which distributes it. And once having reached its target human, then it must there be resistant to attack by natural defence mechanisms of the body, by some effective vaccine or by some other counter-measure. Finally, biological weapons do not respect national or any other artificial frontier; just as the German troops found when the prevailing winds of the Western front blew back their chlorine over their own lines, many of the agents of chemical and biological warfare can be two-edged weapons.

Already biological engineering has reached such a stage that it is possible to tamper with the genetic material of bacteria and viruses so that their fundamental characteristics can be altered; their infectivity, for example, may be increased or decreased. It is now considered that one day it will be feasible to *mask* these organisms so that they will not be recognized by the antibodies which normally resist them in the human body; when this has been done, a live particle will exist which can multiply in its host, and against which the host will have no pre-existing immunity. What will make the particle more insidious is that no method of early warning, leading to some form of defence, will be available to whomever is made to suffer it since its characteristics will have been *masked* by the attacker.

A breakthrough of a second kind is considered to be hanging some way over the horizon. When the cells of the human body are damaged in any way, the body counters the damage by producing enzymes which are capable of making good the injury: in other words, the body has its own inbuilt first-aid shop. If it were possible to produce another enzyme, or some other substance which could *neutralize* this natural reaction, then the body would be robbed of its method of repairing any damage whatever done to it: the first-aid shop would have been abolished. It would not matter whether the injury was caused by bacteria or by the day-to-day wear and tear which the body has to counter from birth. The disease produced by such an agent would be a continuous multiplication of every tiny natural shock that flesh is heir to.*

*R. W. Reid: Tongues of Conscience, 1969.

Septic Shock

in Obstetrics and Gynecology*

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SHOCK DENOTES a clinical syndrome characterized by periods of prostration and hypotension, usually accompanied by pallor, coldness and moistness of skin, collapse of superficial veins, decreased cardiac output, suppression of urine, and definite mental changes. Shock may be produced by several unrelated causes such as hemorrhage, endotoxins and trauma. Endotoxin shock is now widely accepted as a definite clinical entity. There is some confusion between septic abortion and septic (endotoxin) shock. Septic[1] abortion is one associated with an elevation of temperature to 100.4°F (38°C) or more caused by uterine infection on two days, not necessarily consecutive, or a single elevation to 102°F (38.9°C) or more. About 0.1 to 3 percent of septic abortions progress to septic shock.[2] The lesson to be learned is that all abortions are potential candidates for this dreaded complication and only by exercising constant vigilance can prophylaxis be employed to prevent it.

Epidemiology

In obstetrics, endotoxin shock is most often seen in association with criminal abortion, infected spontaneous abortion, secondary to chorioamnionitis, pyelonephritis and puerperal infection, whereas in gynecology it is most frequently associated with pelvic inflammatory disease, pelvic abscess or sepsis associated either with gynecologic cancer or with its treatment. Bacteremia shock occurs at all ages but is observed mainly in elderly patients or in pregnant women.

Endotoxin shock is becoming increasingly important in the field of obstetrics and gynecology. Nowhere in medicine have the research-oriented doctor and the clinician worked

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closer together than in this field. The result has been a drop in the mortality from 80 percent to as low as 11 percent in some series. The proud role of the clinician has traditionally been in the treatment of disease; and patient survival measures his success.

Pathogenesis

In order to appreciate the problem it is important to have a basic familiarity with the pathogenesis of endotoxin shock. In overwhelming infections[3] due to gram-positive bacteria, shock is primarily due to vasodilation and extravasation of fluid, whereas in gram-negative bacteremia neither fluid loss nor vasodilation is the primary cause of hypotension. Clostridial bacteria produce exotoxins which are proteins acting as enzymes producing hemolysis, muscle necrosis and kidney damage. The problem has been well worked out in laboratory animals but has not been as well defined and clarified in the human. There are three major points of view, none of which excludes the others.

Vasoconstrictors

One group believes that endotoxins liberate catecholamines, which are powerful vasoconstrictors. A selective vasospasm results, with the action most intense on the venous sphincters distal to the splanchnic pool* and resulting in a decreased venous return to the heart. The following sequence leads to decreased tissue perfusion, ischemia, cell anoxia, acidosis and ultimately tissue death. A point is reached where stagnant, and hence, irreversible shock occurs. However, in order to dispel gloom and provide an optimistic approach, the concept of irreversible shock should be banished from the mind of the clinician. Let it remain as an autopsy diagnosis.

Intravascular Coagulation

The second concept is that of disseminated intravascular coagulation. McKay[4] injected bacterial endotoxin into pregnant rats and produced a classic Shwartzman phenomenon. In the non-pregnant state an initial injection (preparation phase) is required before a second or provocative dose of endotoxin causes the appearance of thrombi in renal glomerular capillaries. It is of particular interest that pregnant animals required only one injection of endotoxin to produce the glomerular thrombosis. McKay theorized that the intravascular clotting with widespread fibrin deposition produced decreased venous return and subsequent shock. The research supporting each method, although enlightening, has been based on either dog or rat experiments. Cavanagh,[5] on the other hand, has reported his results following production of endotoxic shock in the subhuman primate. The most striking hemodynamic effect was the prompt and marked fall in the renal artery flow within three minutes after injection of E. coli endotoxin. The kidney appears to be the primary target, with the fall in artery flow due not to the reduced aortic pressure but rather to the specific effect of endotoxin on the renal vasculature.

Loss of Vascular Tone

The last theory and the one receiving least support is that of generalized loss of vascular tone.[6] Undoubtedly, this may represent a very late stage in the development of septic shock and may be the final one before irreversible shock.

Diagnosis

An awareness of the situations in which the problem of endotoxin shock can arise will alert the responsible physician to this danger. In large metropolitan hospitals the patient usually presents as an advanced case; it is to this group that the following discussion will be directed. Although diagnosis and management are considered separately, time makes it necessary that these two functions overlap. The emergency nature is not too dissimilar to that of the diabetic presenting with hyperglycemic shock. At the time that the initial blood work is drawn for laboratory evaluation, the treatment must be started. Recognizing that there must be an overlap in the interest of optimum therapy for the patient, it is now possible to discuss diagnosis and management separately.

History

The history is important to identify the pa-

*This type of pooling has not been observed in the monkey or in man. Still, pooling of blood in some area within the venous system is the basic mechanism which accounts for the circulatory shock.

tients at risk; but even if the patient gives a complete story, it is often impossible to obtain an admission of interference either by the patient herself or someone else. Observation of the patient with particular emphasis on recording pulse, blood pressure, respiration and urinary output will help clarify the nature of the problem and indicate whether aggressive therapy is necessary.

Laboratory Studies

There are certain laboratory tests that are indicated: a complete blood count; a platelet count, serum fibrinogen titer; urine for analysis, culture and bilirubin; Na, K, Cl, CO_2, Ca, ph, pCO_2, lactic acid; urea nitrogen; blood volume studies; blood for toxicologic studies; gram-stained smears of the cervix, blood and placental tissue; blood cultures; the inoculation and sealing of a tube of milk to evaluate for Clostridium welchii; an x-ray of the abdomen and chest; and a Douglas test*.

Fluid Stress Test

In order to rule out the problem of hypovolemic shock, a fluid stress test and the response to mannitol should be carried out. The fluid stress test is accomplished with the rapid five-minute infusion of 200 ml. of a crystalloid (electrolyte) solution. If the central venous pressure is not increased more than 5 cm. of water and returns to about 2.5 cm. above the first reading, more fluid can safely be given. A favorable response to mannitol shows that the kidneys are still able to respond. The urinary output should be measured every 15 minutes.

Platelet Count Drop

There is probably no specific test that confirms the diagnosis. A drop in the platelet count and serum fibrinogen titer indicates a very ominous situation. The blood culture is found to be positive in only about one quarter of the cases. An appreciation of the concept of endotoxin would serve to confirm this observation. Endotoxin is a lipopolysaccharide which is found in the cell wall of gram-negative and some gram-positive bacteria; it is released when there is disruption or disintegration of the cell. It is the release of the endotoxin into the blood stream that alters the physiology of the organism and produces the classic picture of septic shock. Spink[7] and Braude report that the shock may be related to the explosive reaction between a component of blood and the endotoxin, thus triggering the phenomenon which resembles an antigen-antibody reaction of the anaphylactic type.

*0.1 ml. of 1:1000 epinephrine is placed intracutaneously in the abdomen of a rabbit; 7 ml. of the patient's plasma is injected into an ear vein. An area of hemorrhagic necrosis developing at the site of epinephrine injection is strong evidence of endotoxin in the plasma sample.

Therapy

The American College of Obstetrics and Gynecologists has published in their Technical Bulletin[8] some excellent guide lines for therapy. Their outline of management has been followed during the past year; among the cases so managed have been endotoxin shock following a curettage, ruptured membranes, pyelonephritis and pelvic infection associated with gynecologic cancer. The plan presented by the College distinguishes between the primary treatment, whether surgical or medical, in which the aim is to eradicate the source of infection. The second aspect is the supportive treatment which will not in itself cure the patient, but will maintain the status quo until the disease is eradicated by the surgical or medical primary therapy, or until the endotoxins are controlled by the reticuloendothelial system. The keynote in therapy is time, as well as vigorous and well-planned treatment. With modifications, the method of management suggested by the College is presented:

Primary Therapy

One doctor must assume full responsibility for the care of the patient.

Surgical Treatment

Prompt evacuation of the infected products of conception or other infected tissue. In more than 90 percent of the cases, only a curettage (D & C) will be required.

Hysterectomy is Indicated if oxytocins fail to evacuate a uterus that is 12 to 14 weeks gestational-size or larger. In the presence of infections, oxytoxic stimulation is most often unrewarding; if there is pus and/

or blood on cul-de-sac aspiration; if there is an adnexal abscess; if there is failure to obtain a significant amount of tissue at the time of curettage; if the patient fails to improve within four to eight hours after curettage; if there is septic shock due to Clostridium welchii, the persistence of infection in the presence of a urinary shutdown, progressive deterioration with a falling fibrinogen titer and platelet count.

Medical Treatment

Medical treatment is employed concomitantly with surgical eradication or alone if the disease cannot be surgically eradicated, as found in pyelonephritis.

Antibiotic regimen per 24 hours is prescribed in accordance with the infecting organism.

Regimen I: penicillin 40 to 50 million units intravenously; chloromycetin 3 to 6 grams intravenously; streptomycin 1 to 2 grams intramuscularly. The reports of blood dyscrasia have served to discredit chloromycetin, but in many instances this regimen has been lifesaving. It is to be borne in mind that K penicillin contains 1.7 meq. K per million units of penicillin.

Regimen II: This regimen is particularly good in untyped gram-negative infections. Kanamycin is particularly active against proteins.

Kanamycin 500 mgm. intramuscularly at the start of therapy followed by 250 mgm. every eight hours; Keflin 4 to 8 grams intravenously.

Regimen III: For Proteus and Pseudomonas Garamycin is particularly active: Garamycin (gantamicin sulfate) 0.8 to 1.5 mgm. kilogram/day intramuscularly in two to four equally divided doses for no longer than eight to 10 days; Keflin 4 to 8 grams intravenously.

Regimen IV: Colymycin (colistin sulfate) 120 to 300 mgm. (2 to 5 mgm. per kilogram) intramuscularly in two to four divided doses; Ampicillin 6 to 12 grams intravenously. Colymycin is particularly active against pseudomonas.

Regimen V: Polyvalent gas gangrene antitoxin 60,000 to 100,000 immunizing units every two to four hours. Penicillin 30 to 50 million units intravenously; chloromycetin 3 to 6 grams intravenously; streptomycin 1 to 2 grams intramuscularly.

Supportive Therapy

1. Volume replacement: fluids, electrolytes, blood, plasma. The central venous pressure serves as a guide to the amount and rate of administration.

2. Correction of acidosis: any fluids containing lactate must be excluded because lactic acid is already accumulating.

3. Corticoids (pharmacologic doses and not as replacement) must be given in equivalent to 1 to 2 grams of cortisone in 24 hours; methyl prednisolone (solu-medrol) 120 to 240 mgm. directly as a bolus intravenously and then 60 to 120 mgm. in each liter I.V. fluids; dexamethasone 40 mgm. intravenously initially, then 20 mgm. intravenously every four to six hours; hydrocortisone 1 to 2 grams intravenously per 24 hours.

4. Administration of digitalis or digoxin as needed.

5. Vasopressor agents: Agent with both alpha and beta mimetic properties—metaraminol (aramine) 100 to 200 mgm. per 500 ml. of intravenous solution. In certain elderly patients it is important to maintain a blood pressure of at least 80 systolic or within 30 mm. of their normal pressure in order to prevent a coronary occlusion or a cerebral accident. This is one of very few indications for vasopressors in shock.

6. Vasodilators: Since most of the problem is due to vasoconstriction and increased peripheral resistance, vasodilators are indicated except as noted above; chlorpromazine (thorazine), promazine (sparine) and triflupromazine (visprin) 2.5 to 5 mgm. directly intravenously and then from one to six hours, if needed; isoproterenol (Isuprel) 2.5 mgm. per 500 m.l. of glucose and water given at the rate of 0.5 to 2 ml. per minute. This seems to be the vasodilator chosen.

7. Hypothemia: Has little application since many of the advanced cases have a drop in temperature. However, in the early stages of sepsis, a cooling blanket provides comfort to the patient.

8. Hyperbaric oxygen: Select cases of resistant Clostrium welchii should be treated in this manner. In general, there is little indication for the use of hyperbaric oxygen.

9. Nasal oxygen.

10. Constant controlled nursing supervision.

The indications for the use of vasodilators are listed: 1. hypotension where volume replacement is normal; 2. diminished organ perfusion as evidenced by diminished urinary output (prefaced by the acceptance that volume replacement has been adequate); 3. prior initiation of correction of acidosis; 4. evidence of peripheral constriction (clinical findings of cold, clammy skin); 5. central venous pressure that is normal or elevated; 6. exaggerated response to fluid stress test; 7. diminished cardiac output; 8. If central venous pressure becomes inordinately elevated without clinical improvement after an infusion of low volume dextran, the patient will respond to an infusion of isoproterenol and, conversely, if the patient responds poorly to isoproterenol, she will be a candidate for low molecular weight dextran; 9. In very critical cases, where other measures have appeared to fail, a cautious trial of isoproterenol (isuprel) is justified.

The first impulse of the clinician faced with this problem, particularly if it is not a common one, is to throw up his hands. His mind is overwhelmed by the impression that many electronic gadgets are needed to control the treatment and check the patient's progress. Nothing is farther from the truth. Lillihei has reduced the control of these patients to clinical observation with help from the routine laboratory. His evaluation is summarized as follows:[10] 1. Peripheral resistance—Examine the patient —If cold and clammy, the peripheral resistance is increased; 2. Blood volume—Observe the central venous pressure. Circulating blood volume is more important than the findings of the peripheral blood volume; 3. Cardiac output—A narrowed pulse pressure correlates with a decreased cardiac output. A fast thready pulse indicates that there is incomplete filling of the heart with a diminished output; 4. Visceral organ blood flow—Measure the output of urine. The urine output is proportional to renal blood flow. Since the kidney is the target-sensitive organ and the renovascular bed is particularly sensitive as far as response to endotoxin is concerned, it is obvious that if the kidney is responding, as evidenced by an adequate urinary output, the other organs are being adequately perfused.

It is obvious that a well informed clinician can treat a seriously ill patient suffering from endotoxin shock with minimal electronic equipment and laboratory reports.

In summary, it is important to treat these patients early and vigorously. One staff member must assume the responsibility and control the patient until recovery is complete. A well coordinated plan of diagnosis and treatment must be followed. The judicious use of a central venous pressure catheter[11] is perhaps the keystone in judging therapy and the response of the patient. Most failures are reflected in the too-little and too-late philosophy. Overloading after initial correction of deficits must be guarded against constantly.

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Medicine is a science of uncertainty and an art of probability.—William Osler.

Medical Terms and Their Lay Synonyms

(Continued from March issue*)

C

Cabbage—*head*
Cachectic fever—*kala azar*
Calf eyes—*strabismus*
Caligo—*cataract*
Camp fever—*typhus fever*
Canker rash—*scarlet fever*
Caps—*capsules*
Capula—*cranium*
Carcass—*human body*
Cardiac asthma—*pulmonary congestion*
Carrion's disease—*bartonellosis*
Cartwheel—*convulsion*
Cartwheel eye—*cataract*
Cascade—*vomit*
Casket filler—*human body*
Casket nails—*teeth*
Castor oil merchant—*physician*
Cat—*to vomit*
Catamania—*menstruation*
Catarrhal pneumonia—*bronchial pneumonia*
Catarrh of the bladder—*chronic cystitis*
Catch in the back—*lumbago*
Catch in the side—*pleuralgia*
Caul—*omentum*
Cauliflower cancer—*cancer of the cervix*
Cellophane—*epidermis*
Cerebral spinal fever—*meningiococcal meningitis*
Cervical rheumatism—*spasm of the cervical spine musculature*
Ceylon sore throat—*sprue*
Chafing—*excoriations*
Chagris fever—*malaria*
Chalk—*scar*
Chamber lye—*urine*
Chanch—*syphilitic chancre*
Chank—*syphilitic chancre*
Change of life—*menopause*
Charbon—*anthrax*
Charley horse—*muscle spasm*
Chasm—*throat*
Chatters—*teeth*
Chest pounder—*physician*
Chicago diarrhea—*amebic dysentery*
Chicken pox—*varicella*
Chilblains—*painful cold extremities*
Childbed fever—*puerperal sepsis*
Child crewing—*glottic spasm*
Chimney sweeper's tumor—*scrotal cancer*
Chin cough—*pertussis*
Chiragra—*gout*
Chiro—*chiropractor*
Choak—*laryngitis*
Chokes—*air embolism*
Choking quinsey—*anthrax*
Chronic catarrh—*chronic bronchitis*
Churchyard cough—*tuberculosis*
Cider—*epsom salts*
Circus—*operating room with gallery*
Clack—*belch*
Clap—*gonorrhea*
Claret—*blood*
Clergyman's knee—*infrapatellar bursitis*
Clergyman's sore throat—*pharyngitis*
Climatic bubo—*lymphopathia venereum*
Climatic fever—*malaria*
Closed for business—*constipated*
Cloth ear—*deaf*
Clovus—*verruca*
Clyers—*actinomycosis*
Clyster—*enema*
Coast fever—*malaria*
Cochen leg—*elephantiasis*
Cochic China diarrhea—*sprue*
Cock's tumor—*suppurating sebaceous adenoma*
Cocoa—*yaws*
Coconut—*skull*
Cold in the head—*rhinitis*
Cold on the breast—*influenza*
Cold on the lungs—*acute bronchitis*
Cold creeps—*chills*
Cold shivers—*chills*
Cold sore—*herpes simplex*
Colitis—*dysentery*
Collapse—*pneumothorax*
Collapse patient—*patient with a pneumothorax*
Collar bone—*clavicle*
Colly wobbles—*abdominal pain*
Colorless corpuscles—*leukocytes*
Come around—*to menstruate*
Come through the front door—*cesarean section*
Coming down of the body—*procidentia*
Coming of the milk—*pre-delivery lactation*
Compressed air sickness—*caisson's disease*
Compression of the lungs—*atelectasis*
Con—*tuberculous patient*
Congestiva—*lupus erythematosus*
Conk—*brain*
Consumption—*tuberculosis*
Contagious eruptive fever—*alistrim*
Coot—*louse*
Copper nose—*acne rosacea*
Cork poppers—*laxatives*
Cork screw—*vertebral column*
Corn husker—*chiropodist*
Corns—*verruca*
Corporocity—*human body*

*See page 286.

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Septic Shock*

Complications Encountered by the Anesthesiologist

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THE VENOUS PRESSURE does not reflect blood volume but indicates the ability of the heart to accept and expel blood returned to it. It reflects the relationship between the blood volume and cardiac competency. In this sense, venous pressure monitoring becomes one of the most useful guides in the management of the patient in shock.

Venous Pressure

Venous pressure may be measured by the indirect as well as the direct method. The indirect technique will measure the peripheral venous pressure only, while the direct approach will determine the more exact central venous pressure.

Indirect Measurement

The indirect method is the simplest means of estimating venous pressure. The heart level is taken as the point of zero venous pressure and lies midway between the dorsum of the thorax and the xiphoid process of the sternum. In the supine position, the arm may be raised from the zero position until the veins on the dorsum of the hand collapse. The height at which this occurs is the venous pressure. Another technique for measuring venous pressure indirectly is by observing venous distention in the neck or any other peripheral vein.

Central Venous Measurement

Central venous pressure measured by means of a catheter placed as close to the right atrium of the heart as possible constitutes a more reliable guide to the state of the circulation. In addition, a centrally placed catheter provides a channel for blood and fluid replacement for a prolonged period of time, without damage to the vessel wall, and can be used for blood sampling or phlebotomy if necessary. Placement of the catheter must, of course, be done under aseptic conditions to avoid bacter-

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emia or thrombus formation.

Technique

Usually a 30-inch, large-bore polyethylene catheter is inserted into a suitable vein either by cutdown or percutaneous technique. The veins generally employed are the median basilic, the superficial jugular, the subclavian or femoral. Employing continuous monitoring of the electrocardiogram, the catheter is advanced until the right atrium is reached. Should arrhythmias appear, the catheter is withdrawn 2 to 3 cm. since it may have inadvertently entered the right ventricle. Many permanent and disposable central venous pressure sets are now available for general use.

Normal Values

Normal venous pressure ranges from 4 to 10 cm. of water but may vary considerably. A pressure above 20 cm. of water strongly suggests myocardial incompetence whether or not blood volume is expanded. Abnormally high pressures may be found in the presence of pericardial tamponade, vena caval obstruction, tension pneumothorax, or during prolonged positive pressure respiration. It is thought by many investigators that a low central venous pressure is of little diagnostic value except that it may indicate a diminished blood volume.

A useful test for estimating possible cardiac failure has been postulated. Administer intravenous fluid in 100 cc. increments every five minutes, measuring the venous pressure after each increment. If the venous pressure does not rise more than 5 cm. within five such trials and return to within 2 cm. of water of the original value, cardiac failure is unlikely.

Sequelae

Although the technique of placing a central venous pressure catheter is comparatively simple, it is not without possible difficulties and complications. Serious infections and thrombotic phenomena have been reported. Peripheral veins have been ruptured, the superior and inferior venae cavae have been lacerated, excessive fluid has extravasated into the neck through a perforated jugular vein, causing respiratory obstruction.

In addition, the right atrium and ventricle have been perforated and heart valves lacerated; and serious arrhythmias have been reported. However, these complications have been few and should not prevent the use of central venous pressure monitoring wherever it is indicated.

Postoperative Complications

Postoperative complications may involve any and all systems of the body, and their development may have begun even during the preoperative period. It will be possible at this time to touch only on those problems which are the primary concern of the anesthesiologist.

The first areas in which postoperative complications may be detected are the recovery room and the surgical intensive care area. The establishment of these locations is one of the most important advances in the care of the surgical patient. They are usually located adjacent to the operating rooms and are under the joint supervision of the surgeons and anesthesiologists. The recovery and intensive care areas are staffed with professional personnel particularly trained to recognize early signs and symptoms of cardiovascular, respiratory, neurologic and metabolic complications. Countless patients have been spared additional pain and anguish and the suffering of postoperative complications since the establishment and acceptance of the recovery room and the surgical intensive care areas.

Respiratory

Among the commonest postoperative complications are those dealing with the respiratory system. The minor complications of pharyngitis, laryngitis and tracheitis are well known and elaboration is not necessary. The more serious respiratory complications are atelectasis, bronchopneumonia, pneumonia and pneumothorax; and these must be diagnosed early and treated vigorously. Pulmonary edema is a grave complication usually caused by cardiac failure, airway obstruction or excessive administration of parenteral fluids, including blood.

Excessive pressure of gases supplied to the patient may result in rupture of alveoli with hemorrhage, capillary air embolism or dissection into the interstitial tissues. Insufflation of a liquid volatile anesthetic agent such as ether or halothane may result in intense bronchospasm and pulmonary edema. Accidental intravenous injection of ether and other agents has been reported to have resulted in pulmonary damage, hypoxia and death.

Cardiovascular

Cardiovascular complications run the gamut from simple hypotension, tachycardia and/or bradycardia to frank shock, serious arrhythmias, peripherovascular collapse, and even cardiac arrest sometime during the postoperative period. Embolization in any form may be masked immediately following surgery because of the patient's depressed state. But when signs become apparent, they are often dramatic and may be the forerunners of an irreversible catastrophe.

Neurological complications may begin with the failure to regain consciousness after a general anesthetic. The most important factors in etiology are hypoxia, carbon dioxide excess, and the effect of anesthetic agents on the reticular formation and the subthalamic area of the midbrain. Other miscellaneous factors resulting in neurological complications are cerebrovascular accidents, hypoglycemia, metabolic acidosis, uremia and embolization associated with the postoperative period but only indirectly related to the administration of an anesthetic.

Although the above complications occur because of certain physical or pathologic characteristics of the patient, the drugs employed, the techniques of anesthetic administration, or the supportive measures used, there are other complications which occur with sufficient frequency and serious consequence to make them noteworthy.

Eyes

Injury to the eyes may occur due to careless application of a face mask, administration of volatile agents, preparation of the skin for head and neck procedures, or abrasion of the conjunctiva or cornea by a carelessly held laryngoscope or a watchband on the left wrist of the anesthesiologist.

Nerves

Injury to peripheral nerves is among the commonest causes of postoperative complications. Among the nerves commonly injured are the divisions of the brachial plexus, the ulnar nerve, the radial nerve, the common peroneal and facial nerves. Occasionally these injuries may be associated with surgery; but usually they are due to faulty positioning of the patient on the operating table.

The list of additional accidents resulting in postoperative complications is infinite and cannot be tabulated here. Although it is obvious that postoperative complications are bound to occur, constant vigilance, attention to details, and much tender loving care will do much to maintain them at a minimum.

Beer and Baloney

Aristotle said there are three groups in society, namely, the belly class, the heart group, and the head type. The belly class is interested in beer and baloney, with little capacity to think. The heart group can be swayed by emotional appeals and flag-waving until it reverses itself, as under Marc Antony's oration at the death of Caesar. Only the head type can really do original thinking and make independent decisions. But even the head type also at times succumbs to the heart and belly appeals.*

*Dr. George Crane: The Quotable Dr. Crane, 1968.

Historic Hospitals

(Continued from Page 372)

America are available from the year 1766, and they recount in fine detail the duties of the comptroller, receiving clerk, steward, chaplain, physician, head surgeon, apothecaries, practitioners, wardrobe keeper, and orderlies.

The royal regulations required that the physician and the head surgeon visit the patients twice each day at 5 A.M. and 3 P.M. in summer and at 6 A.M. and 2 P.M. in winter. The regulations further stated that when these officials arrived at the hospital, "the bell will toll three times and an apothecary, a practitioner, an orderly and a nurse with a light will go to the medical rooms who following the physician will do all that the latter should order them."

The head surgeon was forbidden to "prescribe something which is not available nor cannot be had in the hospital. . . . Although he will not omit what is essential for the treatment nor which tends toward the alleviation of the patients since all is obtained with good government, study, and the application of the physicians."

Interesting regulations too numerous to mention were included. One, apparently made before the use of bed pans became general, required that there be "a few beds with holes in order that those who have fractured legs or thighs may stool without moving." Another provided that the hospital be fumigated "an hour after it has become dark, this will be repeated in the morning after finishing the cleaning of the chamber pots, and repeated . . . a short while after closing the windows for the siesta."*

Warren Kump, M.D.
Minneapolis, Minnesota

*Ann Med Hist 35 IV 481, 1942; Louisiana Hist Quart 29, 559, 1946.

Guying Up

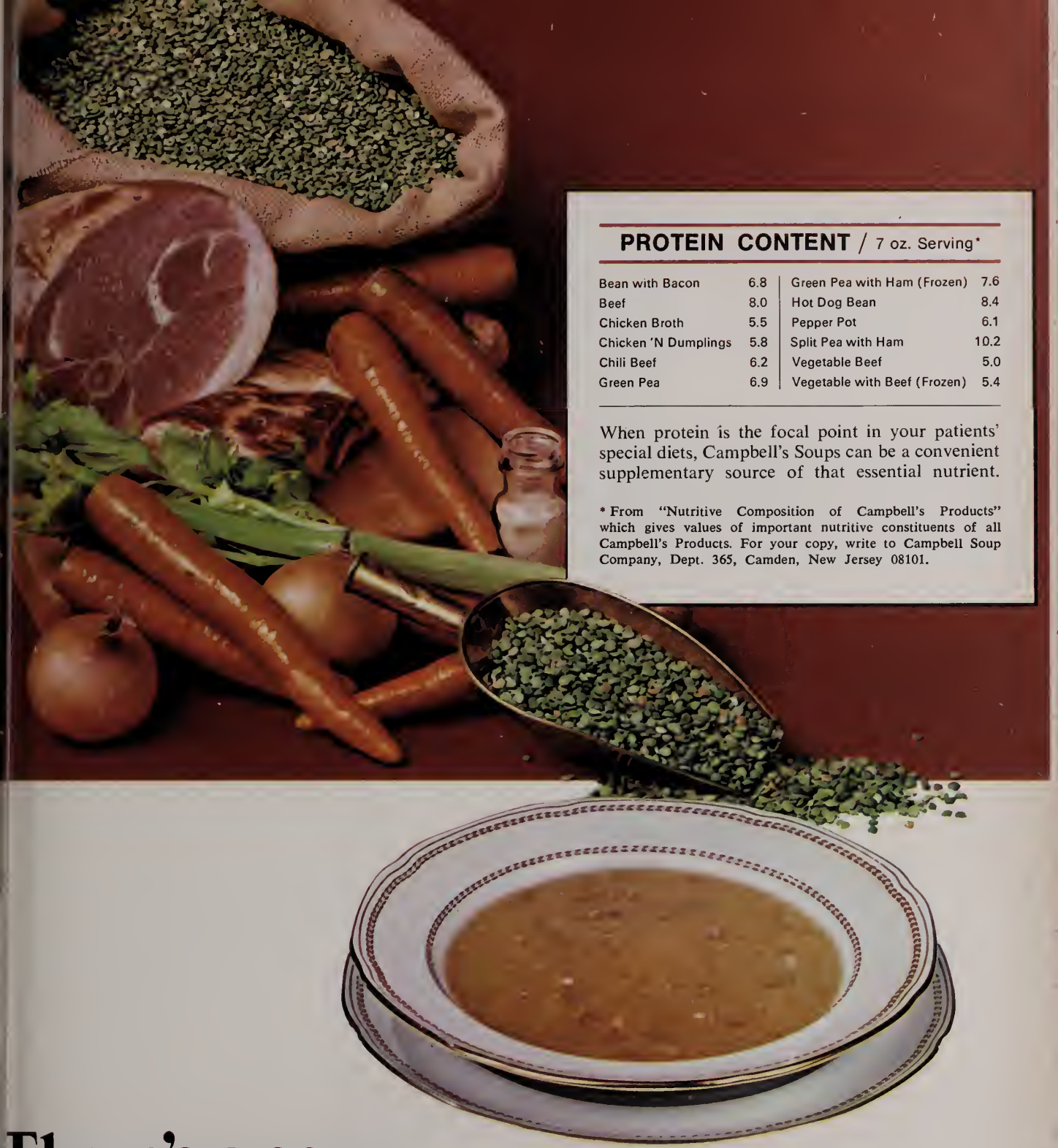
In the more isolated parts of Minnesota's farming belt, neighbors sometimes gather to raise the framework of a barn. On an August day not long ago, the menfolk had reached the crucial stage in such an operation when storm clouds hove up on the horizon. Fearing that a heavy wind might blow the timbers down, the men looked anxiously to the old timer who had taken charge.

"What do you think?" they asked. The old timer looked at the waiting crew, the ready uprights and rafters, and the distant cloud.

"Take her up," he said. "We'll tie the main parts together, and then she'll hold."

Both rafters and people withstand buffeting better when tied together, as our hardy Minnesotans have often proved. A great deal of the strength you mobilize to combat stress and emotional upset comes from others, through interpersonal connections ranging from joint membership in a close-knit group to friendship, blood relationship and marriage. You can find many ways to make those bonds stronger and to gain extra support from them in times of stress.*

*John E. Eichenlaub, M.D.: The Minnesota Doctor's Home Treasury of Unusual Stress Easers, 1964.



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We wish to thank Drs. Marcia K. Bilbao, Louis H. Frische, Josef Rösch and Charles T. Dotter for this exceptionally graphic example of hypotonic duodenography.

Contraindications: Glaucoma, severe cardiac disease.

Precautions: Since varying degrees of urinary hesitancy may occur in elderly men with prostatic hypertrophy, this should be watched for in such patients until they have gained some experience with the drug. Although never reported, theoretically a curare-like action may occur with possible loss of voluntary muscle control. Such patients should receive prompt and continuing artificial respiration until the drug effect has been exhausted.

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982

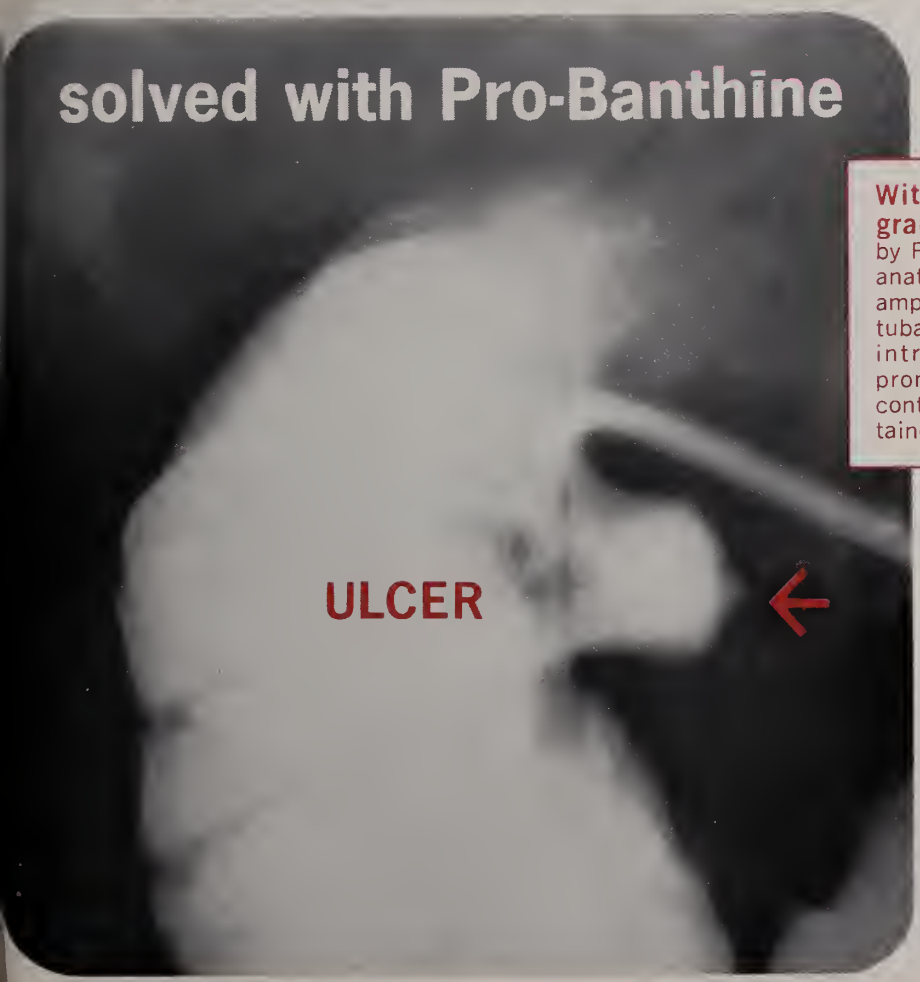
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Editorials

Cancer Therapy*

Restrictive or More Extensive Surgery

In recent years surgery for cancer has become more and more extensive, reaching the point where now the remaining torso of the patient is not much larger than the portion of the body removed: pelvic exenteration, radial pneumonectomy with removal of chest wall, radial mastectomy with dissection of internal mammary chain of nodes, total esophagectomy with colon transplant, and total gastrectomy with hepatic resection. Yet in many of these cases the cure rate is not much different than it was 50 years ago.

This might lead to the question: Shouldn't we now attempt to swing the pendulum towards more restrictive surgery? To this I would have to answer categorically, no, as the old axiom still holds good. Adequate surgical treatment of cancer in the hope of a cure demands *removal of the primary growth, contiguous structures and adjacent lymphatics.* It would seem that the only way that cancer surgery can be made more restrictive and less extensive and still "cure" the patient is in earlier diagnosis and elimination of the delay between the onset of symptoms and definitive therapy.

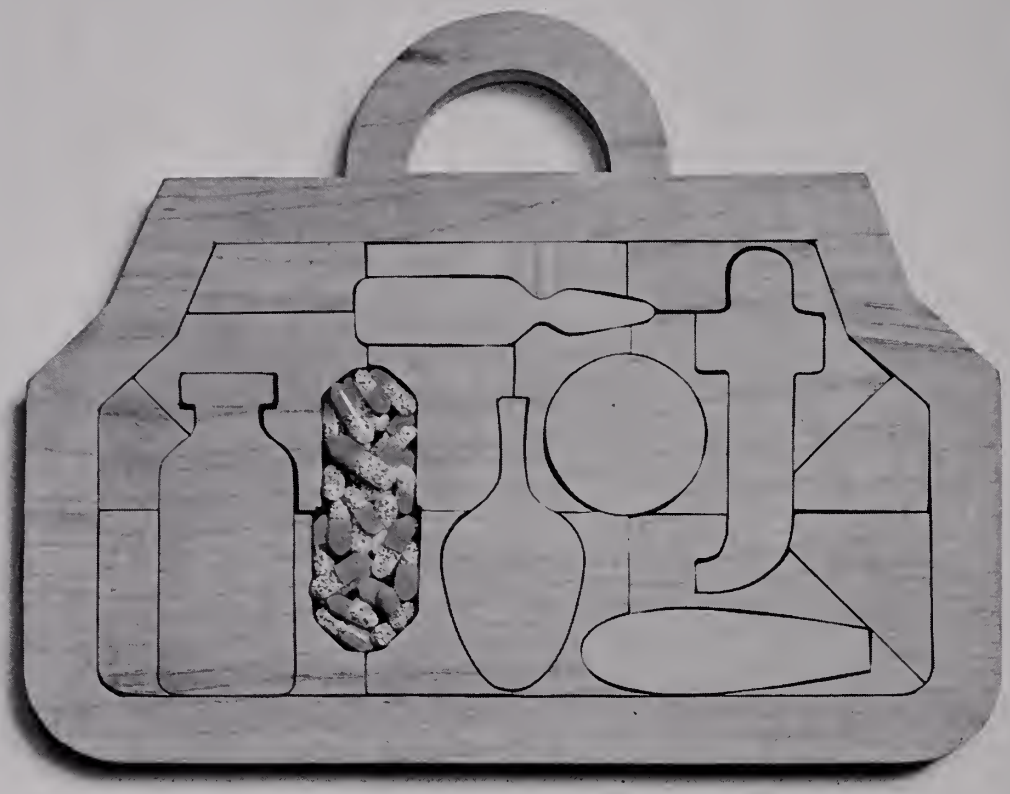
Spread of Cancer

Every surgeon should constantly be aware of the teachings that metastases are spread by direct extension of tumor through contiguity and tissue planes, lymphatic extension, implantation and vascular embolism. It should also be remembered that the vertebral veins drain the lumbar veins, the liver drains by way of the portal system, and the lungs drain by way of the caval system. To aid in the control of these factors, we should be ever mindful of our operative technique. All skin preparations should be gentle, the edges of the wound protected and all unnecessary manipulation minimized. Once operability is determined, the tumor should be isolated with packs, if possible. Frequent changes of drapes, gown, gloves, scalpel, are mandatory in any detailed cancer surgery, as wound seeding is an important factor in local recurrence. There should not only be wide excision of tissue but incontinuity resection whenever possible. Dissection should be directed first to the regional nodes to prevent dislodgement of cells from the primary tumor.

Accessibility

Because of the relative inaccessibility of some organs, curative treatment by radiation and/or surgery is difficult. For example, *carcinoma of the esophagus* shows a distressingly low cure rate, no matter what the treatment. As an organ, the esophagus is readily disten-

*Paper given at the Annual Mid-summer Meeting of the International College of Surgeons in Lake Placid, New York, July 2, 1969.



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sible in the lateral directon. It has no true serosa and its outer layer is longitudinal muscle fibers. Its blood supply is segmental from mediastinal arteries and from the pharyngeal and stomach vessels. In general, the blood supply is sufficiently adequate for the entire esophagus to be mobilized without necrosis, providing the right gastric and the arcades supplying the stomach are not disturbed. Tumor not only spreads to the regional lymph nodes but extends for considerable distances up and down the esophagus. The cardiac nodes about the coeliac axis are frequently involved. Metastasis to the adrenals has not infrequently been found when the local tumor was very small. These patients need hydration, nutritional feedings via gastrostomy if necessary, and often pulmonary care prior to surgery. However, it is essential to operate within a few days whenever possible. Right thoracotomy and laparotomy with complete removal of the abdominal and thoracic esophagus followed by an esophagogastrostomy in the left neck area is our procedure of choice at the present time, though occasionally we have also utilized the colon, both right and left sides as a transplant.

In *carcinoma of the lung,* published reports of survivors so far have not indicated a statistically significant increased cure rate for carcinoma with pneumonectomy and as an incontinuity removal of mediastinal lymph nodes, over just a "simple" pneumonectomy. However, we feel that every effort should be made to remove these nodes. The tendency for metastasis to have occurred beyond the thorax by the time surgery is performed is probably the reason why the statistical reports have been no better with radical pneumonectomy than with simple. This is particularly true in the poorly differentiated cell type tumors and in the patients who initially appear with symptomatic lung tumors. If the tumor is an adenocarcinoma, the patient should be thoroughly worked up, searching for a primary tumor elsewhere. However, multiple primary tumors are not too uncommon, and a solitary lung tumor should always be thought to be a new primary tumor rather than a metastasis.

There continues to be some controversy concerning the treatment of lung cancer by pneumonectomy or lobectomy. Usually the tumor is more localized when lobectomy is the procedure of choice and presumably the disease is less advanced. *Pneumonectomized* patients run a surgical risk of up to 20% depending upon the physiological status of the patient at the time surgery is done, compared to a risk of less than 5% in lobectomized patients. If the tumor could be diagnosed earlier, *simple lobectomy* would invariably be the treatment of choice, with correspondingly decreased morbidity and mortality rates. Simple lobectomy in the coin lesion stage should be possible in 95% of cases; with negative nodes in better than 75% of cases. The resectability rate is increased considerably by the extension of the classic pneumonectomy to include the intrapericardial ligation of hilar vessels plus block dissection of the nodes, i.e., removal of the inferior and subcarinal, as well as the superior mediastinal lymph nodes. As indicated, work-up of lung tumors should include bronchoscopy with washings for cytology and/or biopsy, post-bronchoscopy cough specimens, scalene node biopsy, mediastinoscopy, lung biopsy, tomograms when indicated and, finally, thoracotomy.

Essentially the only patients with lung cancer who survive more than five years after diagnosis are those treated by surgical excision. Studies have failed to show thus far any beneficial effect from any of the chemotherapy drugs used as surgical adjuvants in limited doses.

Harold O. Hallstrand, M.D.
Evanston, Illinois

References may be secured from the author or the reprints.

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Adversity introduces a man to himself.—Anonymous

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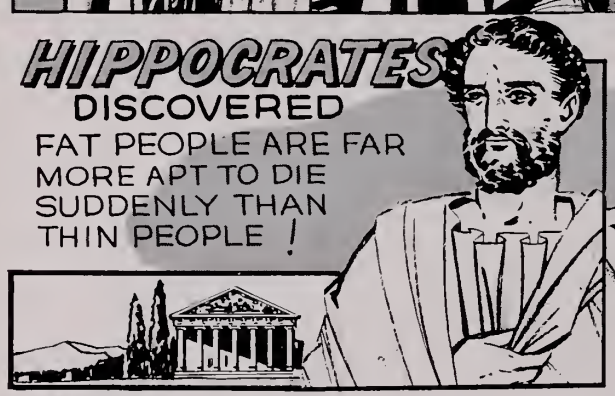
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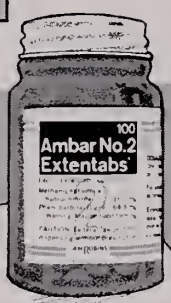
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Micro-Vascular Surgery

Promising New Technique for Coronary Artery Surgery

MICROSURGERY TO CLINICIANS means the use of the dissecting microscope (with magnification commonly in the range of six to 40 times) to carry out procedures which are either impossible or exceedingly difficult, and attended by a high failure rate when performed with the naked eye. Clinical usage of this technique originated largely in surgery of the middle ear and subsequently of the eye. More recently experimental studies in animals indicate a wide variety of potential uses for the technique.

In this issue, Dr. Emil Blair* discusses some of the applications and problems of microsurgery and reports on his own work with peripheral nerve suture in which improved functional results were achieved with microsurgical techniques.

In addition to the applications mentioned by Dr. Blair are many others such as: the experimental use of microsurgical techniques in repair of the ureter, the common bile duct and the pancreatic duct; construction of splenorenal shunts (for use in small children); repair of digital arteries and veins (replantation of severed fingers); reconstruction of the vas deferens and the fallopian tube, and the free transfer of thick skin flaps in plastic surgery.

The advent of microsurgery has resulted in the development of a whole group of "mini" instruments together with suture material which can scarcely be seen with the naked eye. Buncke and Schulz[1] describe the development of a monofilament nylon suture with a thickness of 7.5 micra. The 50-micra needle for this suture is made by metallizing one end of the nylon thread.

Of particular interest to cardiovascular surgeons are the possible applications of these techniques to the problems of human coronary artery disease which is the major cause of death in this country. Encouraging results are now being noted in carrying out bypass grafts of saphenous vein segments between the ascending aorta and the coronary arteries in man distal to points of segmental occlusion or critical narrowing. This introduces additional arterial flow into the coronary arterial tree immediately with concomitant benefits on patient survival and recovery from the symptoms of ischemia. Unfortunately, in a considerable number of patients the larger coronary vessels are not patent or are so severely thickened and calcified that saphenous-vein bypass grafts become extremely difficult or impossible to construct. Micro-vascular techniques would seem to offer opportunities to extend arterial bypass grafting procedures in coronary artery disease, particularly when one considers the well-known tendency for atherosclerosis to involve primarily the larger more proximal coronary arteries while commonly sparing the small distal branches.

Such possibilities are now being explored clinically, as seen in the current report by Edwards et al.[2] in which the distal end of the mobilized left internal mammary artery is anastomosed end-to-side to the distal left anterior descending artery, a vessel of 1-2 mm. external diameter, in patients suffering from intractable angina pectoris, who have severe sclerosis and narrowing or occlusion of the proximal portion of this vessel. Six of seven patients survived the operation with greatly improved exercise tolerance and relief of angina. The one death was apparently due to the development of a fresh myocardial infarction at the time of induction of anesthesia.

Patent anastomoses were shown angiographically three to six months postoperatively in all five patients who have been restudied. Similar results are apparently being obtained by Green[2] of New York in a larger series of operations in which one-year follow-up studies have revealed uniform patency of the anastomoses.

This is an encouraging beginning for the application of microsurgical techniques to the problem of coronary artery disease, but only careful follow-up studies and the passage of time will demonstrate the true value of this approach.

William D. Kelly, M.D.
Minneapolis, Minnesota

*See page 369.
References may be secured from the author or the reprints.

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Central Venous Pressure

A FEW YEARS ago when our faith in arterial blood pressure as the ultimate index of the state of the circulation was being undermined by the use of ganglion-blocking agents in the treatment of shock, the measurement of central venous pressure was seized upon by many of us in the hope that it would supply a magic number upon which our therapies could be based.

In due time, as Dr. Albert Schmookler* points out in this issue, it became apparent that the central venous pressure was not a measure of blood volume nor could it be followed as an all inclusive guide to the state of the circulation. It does, however, provide a valuable bit of information which must be interpreted in the context of the patient's recent history and in association with measurements of arterial blood pressure, pulse and acid base balance.

To Dr. Schmookler's list of problems and complications should be added inaccurate placement of the catheter. Plastic tubes are marvelously able to find their way into the wrong places. One should always be certain that the pressure being measured is in fact "central and venous" before critical therapeutic decisions are made.

Dr. Schmookler's review of the complications that occur following surgery emphasizes the many injuries inadvertently inflicted upon unconscious patients in their treatment. Everyone involved in surgical care of patients should review this list periodically in an effort to prevent the endemic carelessness that tends to creep into routine human activities.

Van Lawrence, M.D.
Minneapolis, Minnesota

*See page 399.

Breast Carcinoma

THE PROBLEMS INVOLVED in the presymptomatic diagnosis of carcinoma of the breast are brought out in an accompanying paper by Henry P. Leis, Jr.* Although the development of simple laboratory screening tests would be of inestimable value, the present "state of the art" of early detection depends on radiographic and thermographic procedures.

Mammography, utilizing the technics of Egan, has been sufficiently popularized so that it is widely and easily available. Since it is easily performed and requires no injections of contrast material, it is readily accepted by the patient. Problems in interpretation do exist, however. Xerography, which replaces the conventional x-ray film with a dry xero-radiography plate, promises to produce mammograms with less radiation and greater detail. Those who have acquired experience with xerography claim that it is easier to interpret and probably offers greater accuracy than conventional mammograms.[1] Unfortunately, to date xerography units are not available on the market. It is hoped that this technical advance will soon be made more widely available.

Since thermography depends on measuring the radiant heat of the subject, no external source of radiation is necessary. The procedure is also said to be rapidly performed and interpreted. Although it has been advocated as a useful tool for population scanning, some conflicting reports as to its efficacy have appeared in the literature.[2]

The success of any detection program, however, may generate other problems. For the proper use of a screening program, large segments of the population will have to be examined. The volume of films generated would probably overload our present supply of trained radiologists. As a partial solution, Alcorn has proposed training nonradiologic personnel to serve as screeners of mammograms.[3] They would function in a manner similar to that of the cytotechnicians now screening Papanicolaou smears. Further studies are under way to determine the feasibility of this proposal.

Marvin E. Goldberg, M.D.
Minneapolis, Minnesota

*See page 355.
References may be secured from the author or the reprints.



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Aura

SOMETIME AGO in MINNESOTA MEDICINE I noted with interest the use of the word "aura" (Latin: air), a term which apparently carries a somewhat different meaning in medical science than in philosophical theory.

According to one Webster definition an aura is a subtle, invisible emanation or exhalation from a substance. Figuratively, a distinctive atmosphere surrounding a person. "There was about her the aura, the glow, the roseate exhalation that surrounds the woman in love." (Edna Ferber). Such auras we are all familiar with: auras of superlative joy, abysmal depression, etc. But they are all transient and usually quite obvious to the ordinary, casual observer. The aura the Oriental philosophy of Hinduism speaks of is also "a distinctive atmosphere surrounding a person" to whom it is attached: always intangible and usually invisible and indefinable except to the adept or the initiate. It is a sheath that envelops and interpenetrates the physical body of a person and constitutes the essence of that person. All that he is is registered therein: the etheric counterpart of himself: a duplicate of his physical, emotional, mental, and spiritual selfhood. It is a permanent attachment and record. Unless one has developed supernormal faculties, one cannot perceive auras. One can judge a person only by his outward manifestations; and appearances can well be deceptive. However, a few of us in the materialistic West do have occasional flashes of insight or intuition into the essence of others; perhaps in eons to come personal auras may become more generally visible to us.

E. R.

Editor's note: In medicine, aura is the peculiar sensation, as of light vapor or cold air, rising from the trunk or limbs toward the head, a premonitory symptom of epilepsy or hysterics, or any other premonitory sensation preceding an epileptic attack.

The distinction between the medical and the philosophic connotations of the word aura are etymologically intriguing and provocative.

Test Your Word Score

Menometrorrhagia—*abnormal uterine bleeding without demonstrable pathologic cause* (page 360).

Habitus—*physique* (page 360).

Ballismus—*a condition marked by jerking and twitching movements* (page 364).

Stereotaxically—*by contact with a solid body* (page 367).

Anisocoria—*inequality of the pupils in diameter* (page 433).

Gumma—*a soft, gummy tumor* (page 433).

Stellate—*star-shaped* (page 434).

Heredofamilial—*hereditary in certain families* (page 437).

Crepitation—*a noise made by rubbing together the ends of a fractured bone* (page 445).

Agenesis—*defective development or absence of any body part* (page 454).

The Editor's Soliloquy

Heartwarming

Answers to our questionnaire were encouraging. I wish I could have written a personal note to all of you who did not leave your address, and thank you for your graciousness. It gives me courage to continue. Your suggestions were excellent and valuable. The figures reveal that you are 50 to 1 in favor of continuing the intellectual character of MINNESOTA MEDICINE. As I had expected you do read a great deal and you do study. Most of you show broad and general interest in the whole field of medicine, regardless of your own restrictive specialty.

Here is a note from an **ophthalmologist** who reads MINNESOTA MEDICINE regularly:

"Take a look at some of the other state medical journals and see what a lot we in Minnesota get for our money! Quality too!"

From a general practitioner: "We do receive more magazines that we can read, but MINNESOTA MEDICINE is one I enjoy and strive to read, even if a month late. The material is generally better than JAMA and I would prefer to have MINNESOTA MEDICINE. If I had some idea what the budget is up against I could probably have more suggestions." *(Incidentally, only $10 of your annual dues are allocated to MINNESOTA MEDICINE and for that you receive the Journal free.—Ed.)*

From an intern: "I think it would be difficult to make many improvements on your excellent Journal. I wish it would come on time." *(That has been a problem with our printer. I can assure you that it will be corrected.—Ed.)*

A doctor in public health suggests: "Reduce other State Medical Association expenditures in order to keep up the support of MINNESOTA MEDICINE." *(Amen!—Ed.)*

From an otolaryngologist: "The highlight in my reading. I use it to keep current. What about the possibilities of a regional journal with the surrounding states?" *(You are so correct and that must be the eventual outcome if a state journal is to remain scientific; but there you have problems: personalities, images, politics, legalities. Come on up and we'll discuss it.—Ed.)*

From a retired surgeon: "I believe that MINNESOTA MEDICINE reaches those who need it most."

From a senior honorable gentleman, former president and outstanding physician: "Keep it up! Editorials excellent!"

From a retired general practitioner: "MINNESOTA MEDICINE should continue because we oldsters need it whether we practice or not." *(With a few notes like that from a half dozen honorable senior citizens how could I ever have been discouraged. I promise to get back on the beam.—Ed.)*

From the Upstate Medical Center, Syracuse, New York: "I read the Journal from cover to cover."

From a dermatologist: "I scan the whole Journal. It is not a bad Journal, nor is it the best. . . ."

From the Ivory Tower: "Specialty issues should be continued. Keep up the series for education. Less advertising." *(Advertising, I know, is a nuisance but it pays for the printing. You pay for the mailing.—Ed.)*

Of course there was a dissenter or two but we're not living in Utopia.*

Your Journal is being widely read; it is also one of the journals that are being read in foreign countries: France, Germany, Norway, Australia. I was delighted with the note from Switzerland; and inasmuch as it came so sincerely from the heart of an outstanding surgeon I quote it verbatim:

(Letter attached)

Bern, den
Erlachstrasse 19
19. Dezember 1969

"Sehr geehrter, lieber Herr Kollege Rice,
Anlässlich des bevorstehenden Jahreswechsels möchte ich nicht verfehlen, Ihnen sehr herzlich zu danken für die mir während des ganzen Jahres zugesandten Minnesota Medicine, welche ich stets mit grossem Interesse gelesen habe. Besonders geschätzt habe ich jeweils die moralisch hochstehenden Sinnsprüche, sowie Ihre persönlichen Anmerkungen.
Allerdings habe ich dieses Jahr keine Zeit gefunden, um Ihnen den seinerzeit zugesagten Beitrag für Ihre Zeitschrift zu senden. Ich hoffe jedoch, dass dies mir im kommenden Jahr möglich sein wird. Gerne würde ich mich dadurch noch erkenntlich zeigen.
Mit den allerbesten Wünschen für Sie und Ihre Familie für die bevorstehenden Festtage verbleibe ich in alter Verbundenheit.

Ihr
Prof. Dr. K. Lenggenhager
Direktor
der Chirurg. Universitätsklinik Bern"

It will cheer your spirits to translate it. It popped my buttons!

Carl O. Rice, M.D.

*Sir Thomas Moore, Harvard Classics.

OLD DOC HESS SAYS: If you seem to be wrangling and using the same words, providing no certainty that you mean the same thing, it might be just as well to say nothing.—C.O.R.

19th Century Failures

Admiral Nelson

Physicians were helpless to control Admiral Nelson's chronic seasickness and dyspepsia, his gastric ulcer and peripheral neuritis. Nor could they alleviate Napoleon's nervous indigestion, edema of the legs during the Russian campaign, or the scabies he contracted during the Italian campaign.*

*The Patient's Progress, Edited by Marti-Ibanez, 1962.

Editor's Note: It is strange that an admiral would continue to pursue his profession on the sea with his chronic seasickness. I would expect that, from his chronic dyspepsia and his peripheral neuritis he suffered from a marked degree of protein deficiency.

Time

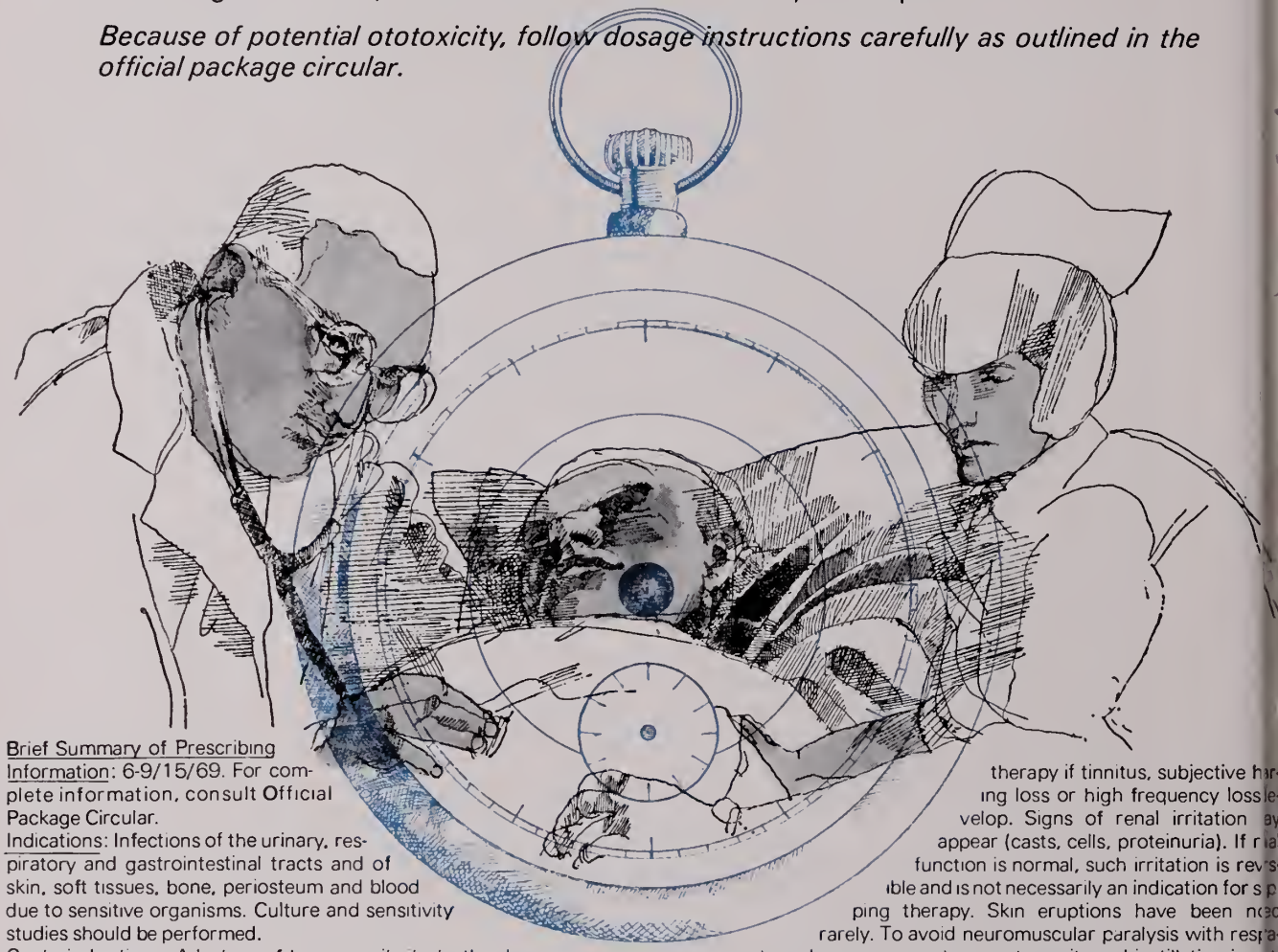
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Precautions: If mycotic or bacterial superinfection occurs, discontinue kanamycin and initiate appropriate therapy. Cumulative ototoxic effects may be produced by concurrent or consecutive use of other ototoxic drugs. High doses may cause irritation at injection sites. The drug *should not* be physically mixed with other antimicrobials.

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The Viewing Box

Left Upper Quadrant Mass

This 31-year-old female was admitted to the hospital with the chief complaint of left upper quadrant abdominal discomfort of two months' duration. The pain radiated to the left shoulder. Physical examination was normal except for a firm left upper quadrant mass. Laboratory examination, including rather complete hematology, revealed only a very mild anemia. The patient had had a cholecystectomy and appendectomy five years prior to admission but the past history was otherwise negative. Intravenous pyelogram reveals a large left upper quadrant mass (Figure 1) with an intrinsically normal left kidney displaced inferiorly.

What is your diagnosis? (See next page.)



Figure 1



Figure 2



Figure 3

Diagnosis: Pseudocyst of the spleen

Because of the generally good condition of the patient and lack of positive physical and laboratory findings a non-neoplastic left upper quadrant mass was suspected. Abdominal aortography (Figure 2) with selective splenic artery angiography was performed which revealed the mass to be avascular and most likely a cyst. Selective angiography in two projections (not illustrated) demonstrated the spleen parenchyma to be located posterior to the large avascular, probably cystic mass.

At surgery a large pseudocyst of the spleen (Figure 3) was found containing 1,300 cc. of partially digested blood.

This type of splenic cyst (post-traumatic) may contain blood in varying stages of digestion, depending on its age. If of long enough standing the contents may become serous and the wall calcified. This is a most common type of splenic cyst. True epithelial cysts are quite rare and parasitic cysts are most common in endemic areas.

Luther O. Wigdahl, M.D.*
Minneapolis, Minnesota

*Department of Radiology, Unity Hospital.

Reference

William J. Forde and Nathaniel Thinby: Splenic Cyst. Clinical Radiology 12:49, 1961.

Guying Up

In the more isolated parts of Minnesota's farming belt, neighbors sometimes gather to raise the framework of a barn. On an August day not long ago, the menfolk had reached the crucial stage in such an operation when storm clouds hove up on the horizon. Fearing that a heavy wind might blow the timbers down, the men looked anxiously to the old timer who had taken charge.

"What do you think?" they asked. The old timer looked at the waiting crew, the ready uprights and rafters, and the distant cloud.

"Take her up," he said. "We'll tie the main parts together, and then she'll hold."

Both rafters and people withstand buffeting better when tied together, as our hardy Minnesotans have often proved. A great deal of the strength you mobilize to combat stress and emotional upset comes from others, through interpersonal connections ranging from joint membership in a close-knit group to friendship, blood relationship and marriage. You can find many ways to make those bonds stronger and to gain extra support from them in times of stress.*

*John E. Eichenlaub, M.D.: The Minnesota Doctor's Home Treasury of Unusual Stress Easers, 1964.

The one thing that hurts more than paying an income tax is not having to pay an income tax.—Thomas R. Dewar

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Curbstone Consultation

QUESTION: What are the incidence and mortality rates of uterine cancer in the United States?

ANSWER: Approximately 16,000 females die of uterine cancer annually in the United States. The following mortality rates were furnished by the American Cancer Society:

In 1930.....28/100,000 females
In 1945.....24/100,000 females
In 1965.....14/100,000 females

The incidence of cervical cancer varies with nationality, location, socio-economic status, age at marriage, age at first coitus, and number of partners involved. It is estimated that 1.5 to 2% of all females develop cancer of the uterus. Clyde Randall reported that for every 100 new cases there are 41.58 deaths. Figures from the Louisville Study in 1965 (N.E.J.M.) revealed the following incidence rate for invasive cancer of the cervix:

62.5/100,000 females in that quarter of the population with the lowest income
25.5/100,000 females in that quarter of the population with the highest income

In various large studies the same general trend has been noted: There has been a marked decline in the incidence of invasive cancer of the cervix with some improvement in the survival rates. Early detection programs are finding more cervical carcinomas in situ and fewer invasive types, which means that more adequate treatment can be started earlier.

Cancer of the fundus was thought to be one tenth as frequent as cancer of the cervix, but today it seems more prevalent, approximately one third to one fourth as frequent. Clyde Randall reported an incidence rate of 17.8/100,000 in 1950 with a mortality of 6.47/100,000.

QUESTION: Have the gynecologists really done anything about reducing the incidence rate of cervical cancer or is it that just more men are circumcised?

ANSWER: Although females married to circumcised males do have a lower incidence rate, the incidence of cancer of the cervix started dropping before the use of the Pap smear. The smear has helped detect more cases of carcinoma in situ and so caused a decrease in invasive cancer of the cervix. Earlier and

more adequate treatment has diminished the mortality and increased the five-year survival rates.

The current concept of viral etiology and our present knowledge of the epidemiology and oncology of cancer of the cervix indicate that cervical cancer is a social disease—a true venereal disease.

QUESTION: Is there any relationship between any gynecological cancers and breast cancer?

ANSWER: There appears to be a relationship, as it is not uncommon for a patient with an apparently successful radical mastectomy for cancer of the breast to develop an ovarian cancer after several years. However, there may be some difficulty in differentiating between a late metastasis and a new primary growth.

Single and nulliparous women appear to have a greater incidence of cancer of the breast and cancer of the ovary. Pregnancy hormones seem to have a protective effect. Both types of cancer occur more often in women over 45 years of age.

Prolonged estrogen levels, especially without breaks or unopposed (as without the use of androgens), may cause changes in the breasts as well as in the endometrium, which can become carcinoma. Cystic mastitis is often associated with dysmenorrhea and menstrual irregularities. Although it has been impossible to determine what per cent of cystic mastitis later becomes malignant, a larger number of cancers develop in women with cystic mastitis than in those with normal breasts.

There is no known association between carcinoma of the breast and carcinoma of the cervix. The former is a disease of women of higher economic status, while the latter is oftener seen in the lower socioeconomic group.

QUESTION: What is the marked reduction in mortality rates on uterine cancer due to? (One half that of 20 years ago)

ANSWER: Although a slight decrease in the incidence of cancer of the uterus was apparent prior to the development and extensive use of the Pap smear, the marked reduction in mortality rates of uterine cancer is due chiefly to earlier detection by cytological screening with annual Pap smears, especially in high-risk groups.

International uniform staging and classification, as well as the development of concepts of what constitutes adequate therapy, has helped evaluate the newer modalities of treatment: improved radiation techniques and the development and use of chemotherapeutic agents, etc. We now are beginning to understand what constitutes adequate and appropriate surgery for each stage of the disease.

More knowledge of the etiology or epidemiology seems to indicate that cancer of the cervix is a preventable disease. Perhaps soon we may find some way of raising host immunity and induce rejection of this foreign tissue. Antigenic preparations may check the spread of or eradicate these malignant cells. Anti-viral vaccines may prevent viral infections and possible development of cancer.

QUESTION: Are there other methods of pre-symptomatic diagnosis of uterine cancer besides the Papanicolaou cytology test? How often should the test be done and what is its accuracy?

ANSWER: Pap smears are positive in 70 to 95% of proved cancers of the cervix. Although the test may indicate the diagnosis when clumps of tumor cells are found, the biopsy or conization specimen gives the true diagnosis. The Schiller test and biopsy alone are positive in 80% of proven cancers of the cervix. Pap smears, pelvic examinations, the Schiller test, and multiple biopsies of the cervix give the highest percent of positives and establish the diagnosis.

Cold-knife conization is useful in doubtful cases to establish the extent of the disease and to rule out invasion, which is important in deciding what the treatment will be. Colposcope examination is not as popular in the United States as in other countries. It has several major drawbacks, since it requires extensive training and experience, and it can also miss the intracervical lesion. Endometrial lavage or brushing has been used as a screening test in high-risk endometrial cancer patients (see text).

Several enzymes are being studied as possible tip-off tests since they are apparently found in the discharge from cancer of the uterus.

Lymphangiography has been found useful only for identification of glands and evaluation of the adequacy of lymphadenectomy.

QUESTION: Can ovarian cancer be diagnosed in a pre-symptomatic stage? What are the incidence and mortality rates of ovarian cancer?

ANSWER: Cancer of the ovary is the fourth leading cause of death from cancer in the United States. Although the mortality rate of cervical cancer has been more than halved since 1930, the death rate from ovarian cancer has more than doubled—from 3.2 to 8.9 per 100,000. Cancer of the ovary is less than one half as common as cancer of the cervix, but its incidence is slowly increasing. To date, however, no reason for this rising incidence has been recognized.

The overall five-year survival rate is only about 27%, due to the fact that in most cases ovarian cancer is found too late; Javert and Roscoe estimated that only one cancer of the ovary without symptoms will be detected in 10,000 pelvic examinations. If the growth can be found when it is limited to the two ovaries the five-year survival rate rises to 50-65%. Again, regular pelvic examinations should be done in high-risk groups (see text). The younger the patient, the earlier the diagnosis, the smaller the tumor, the better the prognosis. In suspicious ovarian lesions, careful needling of the cul-de-sac with aspiration of fluid may confirm the diagnosis or indicate recurrence. Any mass of the ovary over 5 cm. should be investigated by laparotomy.

QUESTION: In case of truly early pre-symptomatic diagnosis of uterine cancer, does this allow for less extensive operative procedures?

ANSWER: Yes, definitely. If the diagnosis is made early, the lesion will be so much less extensive that more limited and less radical treatment can ensure a greater percentage of cure. Even some ovarian cancers that metastasize early have a better chance of cure when found early and completely removed.

Salvatore Traina, M.D.*
Medford, Massachusetts

*See page 357.

To manage men one ought to have a sharp mind in a velvet shield.—George Eliot.

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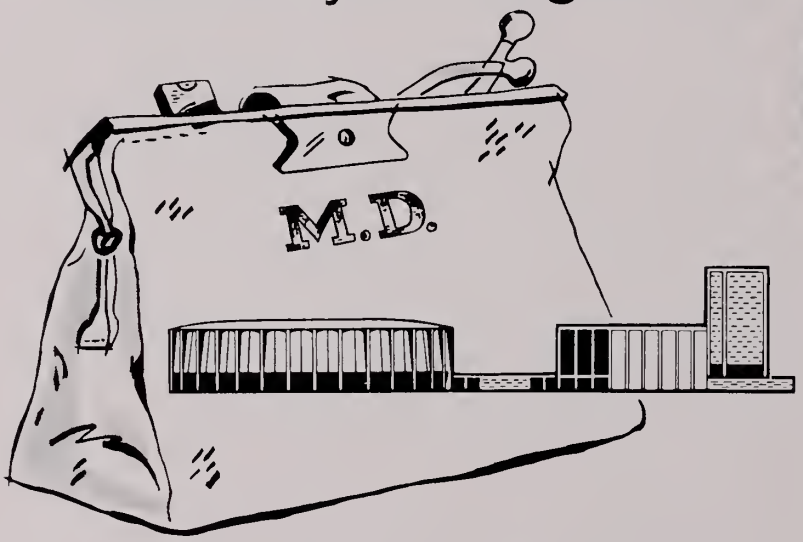
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Clinical Path Conference

Pneumococcal Meningitis and Brain Abscess

History

Dr. William Torp:*

A 63-year-old woman was admitted to the hospital because of unconsciousness. According to her relatives, she had suffered from diabetes mellitus for about five years and this had been well controlled with tolbutamide 2 grams daily. About four weeks prior to this admission she had developed an infection in her left ear which was treated by a private physician with oxytetracycline. Approximately three weeks before admission she had complained of left-sided temporal and periorbital headaches and some difficulty with vision in her left eye. Two weeks before admission it was noticed that she often used incorrect words to name objects (for example, she referred to a pet bird as a cat). Twenty-four hours before admission she had complained of nausea, and the following morning was found semi-comatose at home and brought to the hospital.

Examination

On examination, she was semi-comatose and obese. Her blood pressure was 214/120; temperature 104°; respiration 24/min. and pulse 90 and regular. The pupil of the left eye was larger than that of the right. The margins of the optic discs were sharp and the discs were cupped centrally. There was bilateral scarring, retraction and redness of the tympanic membranes. Her neck was stiff. Bilateral diffuse rhonchi were audible in the lungs. The heart and abdomen were normal. Painful stimuli caused movement of all extremities. Application of painful stimuli to the extremities resulted in their withdrawal; but motion of the left arm and leg was sluggish compared with the right. Tendon reflexes were diminished on the left side of the body and there was an equivocal response to Babinski's test on the left.

Laboratory Studies

The hemoglobin was 16.1 Gm. %; the white blood count 30,200 with 92% neutrophils. The urine was slightly cloudy, with a specific gravity of 1.027, and gave a 2+ test for albumin, a 4+ test for sugar, and a 2+ test for acetone. Fifty-five to sixty red blood cells per high-power field were observed on microscopic examination of the urine. The blood glucose was 465 mg. %; serum sodium 135 mEq/L; potassium 3.7 mEq/L; chloride 91 mEq/L; CO_2 19 mEq/L. Calcium was 10.5 mg. %; bilirubin 1.1 mg. % and blood urea nitrogen 7 mg. %. Total serum proteins were 8.2 Gm. % with 4.3 Gm. % albumin. Serum transaminase was 47 units. The culture of the urine was sterile.

Hospital Course

Roentgenograms of the skull were obtained immediately after admission and were normal. An electroencephalogram was described as markedly abnormal "because of moderate and high amplitude delta and theta activity in the left hemisphere." It was felt by the interpreter that the electroencephalogram was consistent with a destructive lesion in the left cerebral hemisphere.

*Attending Staff, Department of Internal Medicine, Hennepin County General Hospital.

A chest roentgenogram was reportedly normal, as was a supine film of the abdomen. A left carotid angiogram was then attempted and reportedly revealed diffuse spasm of the left cerebral vessels; no specific diagnosis could be made from the films. During the procedure the patient experienced cardiac arrest from which she was successfully resuscitated.

Subsequent neurological examination revealed complete unresponsiveness to pain, and on the "doll's head" test, the patient's eyes did not move fully to the left. Following neurological and neurosurgical consultation another left carotid angiogram was attempted but again felt to be non-diagnostic. Following this procedure the patient again suffered a cardiac arrest. Resuscitation attempts at this time were unsuccessful and the patient died.

Clinical Discussion

This 63-year-old lady was hospitalized approximately 18 hours antemortem in an unconscious state. She had had a five-year history of diabetes mellitus that was well controlled with tolbutamide. Approximately four weeks prior to hospitalization she had developed an infection of the left ear that was treated with tetracycline. One week later she had developed headache and some difficulty in vision in the left eye. Two weeks prior to admission she had developed nominal aphasia, and one day prior to admission, nausea followed by a semi-comatose state. On admission she was semi-comatose but responded to noxious stimuli. Her blood pressure was elevated and there was a marked elevation of temperature. Her pulse was 90 and one might have expected it to be more rapid with the degree of temperature elevation. The left pupil was larger than the right; optic discs were sharp and cupped centrally and were interpreted as probably indicating increased intracranial pressure. There was scarring, retraction and reddening of tympanic membranes. She had a stiff neck and responded to painful stimuli, but less well on the left side. Deep tendon reflexes were decreased on the left and she had a questionable left Babinski reflex. Laboratory studies disclosed a white count of 30,000, 2+ acetonuria, 4+ glycosuria, albuminuria, and 55-60 red cells per high-power field. The urine was sterile on culture. Blood sugar was 465 mg.%. Potassium and CO_2 combining power were both diminished, but the patient did not appear to be in severe acidosis. The blood urea nitrogen of 7 may have been secondary to poor dietary intake. An electroencephalogram disclosed changes consistent with a destructive lesion of the left hemisphere consistent with an infective or neoplastic process. May we have the x-ray now.

Dr. Oscar Lipschultz:*

Angiographic studies disclosed poor contrast in the peripheral vessels consistent with increased intracranial pressure. In addition, the left middle cerebral artery was elevated, a finding that may be associated with a left temporal lobe lesion. There were no other significant abnormalities. Examination of the mastoid areas also disclosed a sclerotic process that could be secondary to a previous infectious process.

Dr. Torp:

During the angiographic procedure the patient incurred a cardiac arrest and, following this, she could not move her eyes fully to the left. An angiogram was repeated and was again non-diagnostic. After this procedure she experienced a second cardiac arrest and expired.

*Staff Radiologist, Hennepin County General Hospital

It is obvious from the clinical history that this patient was severely ill secondary to an intracranial lesion that was manifested by headache, nausea, stiff neck, aphasia and impaired consciousness, and increased intracranial pressure. Because of this a lumbar puncture was deferred. Furthermore, a pulse of 90 might be considered a relative bradycardia in relationship to her markedly elevated temperature; this likewise is consistent with secondary effects of increased intracranial pressure. She had localizing signs on the left side characterized by left-sided headache and a dilated left pupil. The left-sided findings of the extremities probably indicate a shift of the brain structures to the right with impingement on the cerebral peduncle by the tentorium. It is of interest that diabetic patients may manifest anisocoria,* and results of previous examinations would be helpful in interpreting this sign. Although diabetes probably predisposed this patient to infection, I doubt that diabetic acidosis was the basis for her demise.

A differential diagnosis must include several different intracranial processes. One would have to consider a chronic otitis media resulting in a temporal lobe abscess and perhaps a secondary spillage into the ventricular system with diffuse meningitis. Other possibilities include subdural abscess, transverse sinus thrombosis and a primary neoplasm. In addition, metastatic brain abscess is a possibility, although there was no evidence of either subacute bacterial endocarditis or chronic lung disease in this patient. Remote possibilities also include tuberculoma and gumma.*

I think the most likely process is that of a left temporal-lobe suppurative process. Fifty per cent of these occur secondary to middle ear infections, and the second most common cause is that of a metastatic abscess from either chronic suppurative lung process or bacterial endocarditis. There are multiple tracts whereby metastatic infections may develop in the brain; this makes the brain a vulnerable site. The third most common source of infection is from the paranasal sinuses. The most common organisms causing such suppurative processes are staphylococcus, pneumococcus, streptococcus and E. coli. There are many other microorganisms as well, and, not infrequently, mixed bacterial colonies are present.

Because of the proximity of the paranasal sinuses and middle ear to the brain, either improper therapy or insufficient response to therapy subjects the patient to complications and special problems with infections of these structures. In one study 80 cases of brain abscess were attributed to infections of the middle ear. Of these, 52 were in the temporal lobe, with a mortality of 23%. Twenty-five were present in the cerebellar hemisphere and resulted in subdural abscesses. The mortality of these latter sites was approximately one third. Symptoms of headache, decreased level of consciousness, fever and stiff neck were present in more than 60% of these patients, and more than 80% developed localizing signs. In temporal lobe lesions localizing signs were usually contralateral. Visual field defects and nominal aphasia were frequently present.[1]

The patient presented today manifested all of these symptoms. Furthermore, she had symptoms for approximately two to three weeks indicative of a subacute process which is more consistent with a temporal lobe abscess. Subdural abscesses, by contrast, are usually of shorter duration and manifest a more acute course. It is of interest that, although subdural abscesses are much

*See Test Your Word Score page 415.

less common as complications of temporal lobe abscess, nevertheless, they may show much the same symptomatology. The three patients with subdural abscesses in the study cited[1] all had contralateral hemiplegia, nominal aphasia, and visual field defects. In addition, several developed meningitis prior to abscess formation, and this appears to be analogous to the clinical situation in the patient considered today. Since the findings of either subdural or temporal lobe abscess may be quite similar, I find it impossible to differentiate which process was present in this patient. It is entirely possible that a subdural abscess may have developed with subsequent extension into the temporal lobe. I believe the most likely sequence of events was a chronic otitis media complicated by a temporal lobe abscess and probable secondary extension into the ventricular system with diffuse meningitis.

Pathology Discussion

Dr. Robert Anderson:*

At necropsy the principal findings and those of primary interest were in the brain. Upon reflection of the dura, there was a marked degree of purulent exudate over the cerebral convexities. This was most concentrated in the sulci and, in particular, extended the full length of the Sylvian fissure bilaterally. Culture of this exudate yielded mucoid pneumococci that were typical of Type III. This meningeal exudate was prominent over the base of the brain and particularly over the inframedial aspect of both cerebellar hemispheres. In addition, exudate was present over the pons and over the lateral aspect of the left temporal lobe. This lobe was externally quite striking. There was a somewhat stellate,† depressed focus measuring approximately 2 cm. in greatest extent situated in the mid-lateral aspect. The brain parenchyma bordering this was swollen and softened in consistency. Sections through this area disclosed a fairly large abscess cavity that occupied the major portion of the white matter of the left temporal lobe (Figure 1) and measured fully 4 cm.

*Staff, Department of Pathology, Hennepin County General Hospital.
†See Test Your Word Score Page 415.

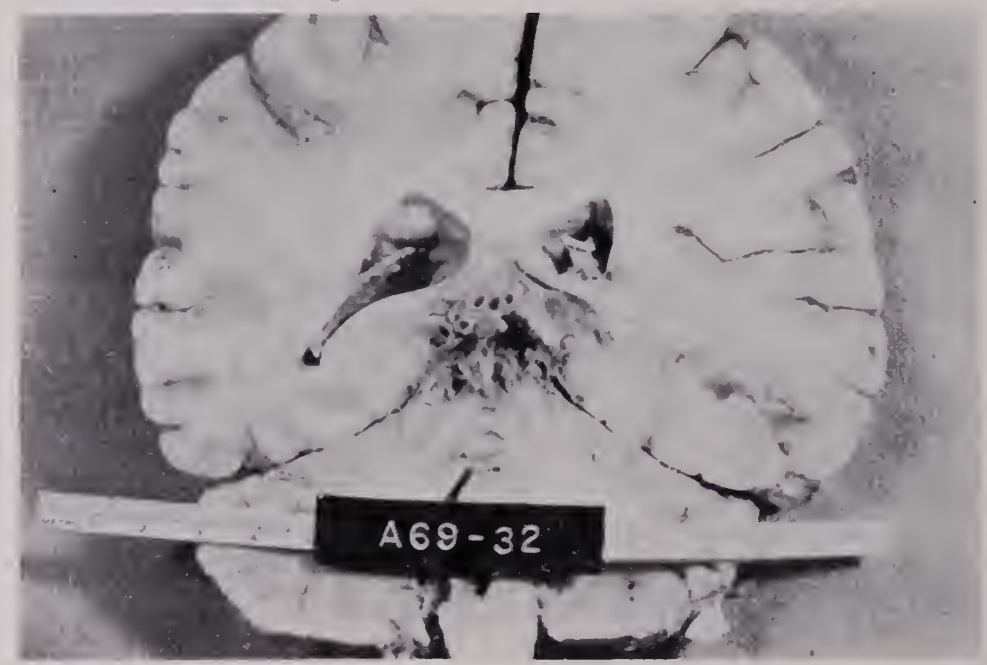


Fig. 1—Coronal brain section showing left temporal lobe abscess extending virtually to lateral ventricle.

in greatest extent. Though well localized, this was unencapsulated, and the marginating brain parenchyma was softened, friable and edematous, resulting in an inframedial displacement of the left hippocampal gyrus. Abscess cavity contents were somewhat mucinous in texture and gray-brown in color.

Prominent thickening and infiltration of meninges by polymorphonuclear leucocytes were particularly striking over the cerebellum where a heavy accumulation of polymorphs was present over and between the cerebellar folia. Cortices for the most part were uninvolved though there were occasional microscopic foci in which there was a superficial leucocytic infiltration. Sections through the intracerebral abscess revealed aggregations of polymorphs and condensed fibrin. Gram stain of these failed to reveal intracellular pneumococci. Bordering the abscess cavity early vascularization was evident indicating early organization. Reactive changes were present in adjacent brain parenchyma that are frequently associated with brain abscesses: an increased cellularity secondary not only to infiltration of polymorphs and round cells but also proliferation of glial elements (Figure 2). In addition, there was a fairly prominent vascular proliferation, and many of these disclosed fibrous thickening of the adventitial portion. Other small vessels were accentuated by cellular perivascular lymphocytic cuffing. Early fibroblastic proliferation was also evident, indicating attempts at fibrous encapsulation. Only in areas bordering the abscess cavity was there destruction of myelin that was limited to the abscess area. Luxol fast blue—H & E stains disclosed degeneration of myelin in these areas and phagocytosis of lipid material by infiltrating reactive microglia and histiocytes.

In our experience intracerebral abscesses have been relatively rare. It is well recognized that these are complications of infections from certain foci; meningitis and brain abscess in particular are dreaded complications of middle-ear infections as well as infections of the paranasal sinuses. Of these, the most frequent source is of the middle ear, and complications from this infectious focus are anywhere from five to ten times as frequent as those from

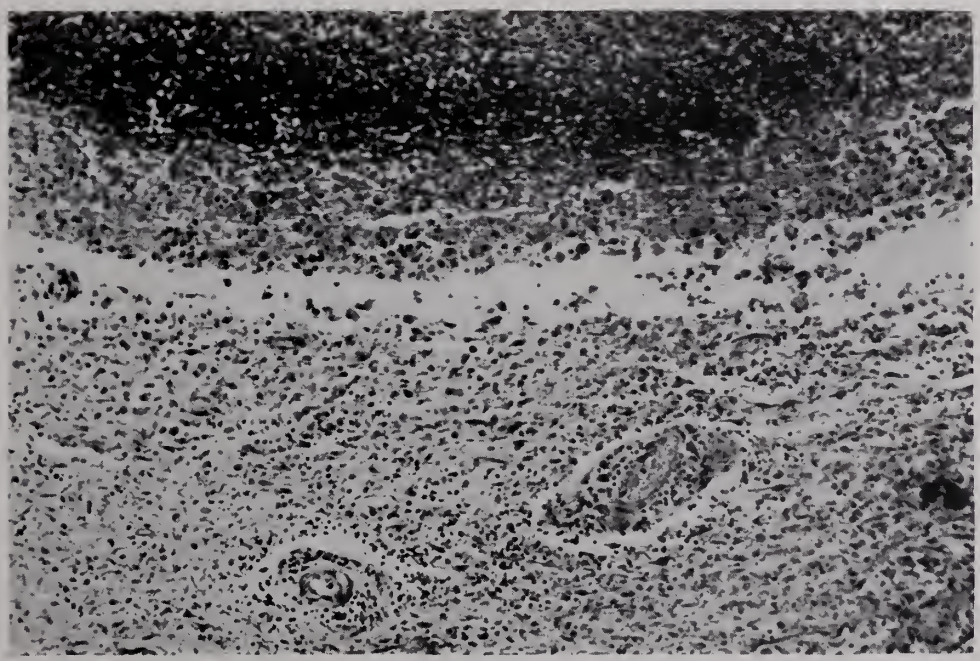


Fig. 2—Wall of brain abscess showing fibrinopurulent exudate (upper) and reactive cellular infiltration and perivascular infiltration in brain parenchyma (lower). H & E x 50.

infections of the paranasal sinuses. In addition, pyemic states and metastases from intrathoracic suppurations such as lung abscesses and bronchiectasis may serve as sources for the onset of intracerebral abscesses. Finally, penetrating head injuries are frequently complicated by both intracerebral abscesses and recurrent meningitis.

It is thought that brain abscesses of otitic origin are transmitted to the brain substance through one of three channels; by septic thrombosis of the transverse sinus, by osteomyelitis of the tympanic wall, or by spread along the adventitial spaces of the small perforating blood vessels. Infections originating in tegmen tympani more commonly localize in the temporal lobe in adults. In children, by contrast, infections of the mastoid air sinuses may be more common, with a tendency to localize in the cerebellum. There are certain sequential stages in the development of the brain abscess, and these have some relationship to its pathogenicity. In the earliest stages, the most we can recognize is an acute encephalitis that is poorly localized and without exudate. With continuance of the infection, purulent exudate develops; but this likewise remains poorly localized. With protracted infection, however, fibrous encapsulation with localization ensues. But abscesses of the brain do differ from abscesses in other sites of the body in that fibrous encapsulation and proliferation are often protracted and poorly formed. As a result, intracerebral abscesses have a greater tendency to spread and may form either satellite abscesses, or rupture either into the ventricular system or into the meningeal space, resulting in a diffuse meningitis.

A wide variety of microorganisms including some parasitic forms have been implicated in brain abscesses; however, the most frequent causative organisms are the streptococcus, staphylococcus, pneumococcus, coliform bacilli, diphtheroids and mixed bacterial forms. In spite of antibiotic therapy, pneumococcal meningitis and brain abscess remain a menace with a significantly high mortality. This was emphasized by Spink and Su in a study of pneumococcal meningitis at the University of Minnesota over a fourteen-and-one-half-year period,[2] during which 55 cases of documented pneumococcal meningitis were studied. An analysis of these patients disclosed several interesting findings. The overall mortality was 25%. With increase in age, however, there was a significant increase in mortality; in patients over the age of 40 years, mortality had increased to greater than 50%. In 18 patients, a preceding pneumococcal otitis media was documented. The paranasal sinuses were less commonly involved. Penetrating head injury and pneumococcal pneumonia were considerably less frequent, each of these accounting for four cases. In 22 patients there was no detectable infectious focus. The patient presented today is illustrative of this persistent menace of meningitis and brain abscess complicating a pneumococcal otitis media.

Dr. Andrew Edin:*

Would the patient's course and outcome have been different had she received a different antibiotic initially?

Dr. Anderson:

Quite possibly, since some pneumococcal infections resistant to tetracycline have been documented.

*Former resident, Department of Internal Medicine, Hennepin County General Hospital.

Dr. Ed Seljeskog:*

An additional category of brain abscess from the neurosurgical aspect that has come to the forefront within recent years has been that seen in a review of children with cyanotic congenital heart disease with right to left shunts. The outstanding features of these brain abscesses are that they are chronic in nature, are usually caused by mixed organisms, and are very large in size. These more frequently occur in the end arteries of the middle cerebral distribution, mainly the parietal-temporal area, and are metastatic in nature. In addition, there has been a relative decrease in the incidence of temporal lobe abscesses due to a decrease in middle-ear disease. The other outstanding feature of this review is that there is no correlation between the organisms recovered from the lumbar spinal fluid and from the abscess cavity proper. A fair number of these patients got into trouble following a lumbar puncture; hence I would like to emphasize that when dealing with intracerebral abscesses, the hazards of performing a lumbar puncture must be considered.

W. Robert Anderson, M.D.
William B. Torp, M.D.
Thomas F. Mulrooney, M.D.
Minneapolis, Minnesota

*Staff, Department of Surgery, Hennepin County General Hospital.

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2. Spink, W. W., and Su, C. K.: Persistent Menace of Pneumococcal Meningitis. JAMA 173:1545, 1960.

Rietti-Greppi-Micheli Syndrome

This form of hemolytic icterus with decreased red cell fragility belongs in the category of Mediterranean hemolytic syndromes of moderate degree. It is a heredofamilial* constitutional disorder that has been observed most frequently in Italians but also in other residents of the northern Mediterranean coast. Scattered cases, occurring perhaps through heredity and migration, have been reported in various parts of the world.

Erythrocytes are elliptoid, exhibit poikilocytosis, and show increased osmotic resistance to hemolysis and decreased red cell fragility. The intense erythrocytic disintegration is accompanied by signs of increased mechanical fragility. According to Marmont and Bianci, pathologically increased mechanical fragility occurs only in iron-deficient anemias.

The pathologic process varies from a barely perceptible abnormality of the red blood cells to a severe degree of anemia, icterus, and splenomegaly. It resembles or at least has many analogous features of Cooley's anemia; however, variations in the clinical pattern and characteristics make it difficult to classify these cases.

The pathogenesis of the syndrome is speculative. A congenital error of iron metabolism is suspected, involving perhaps faulty stromatohemoglobin bindings. This deficiency is sometimes described as metabolic dyserythropoesis. Although the course is benign, therapy is difficult. As a rule these patients are iron resistant, even to iron given by the intravenous route.

Durham, Robert H.—Encyclopedia of Medical Syndromes
Hoeber Medical Division, Harper and Row, New York

*See Test Your Word Score page 415.



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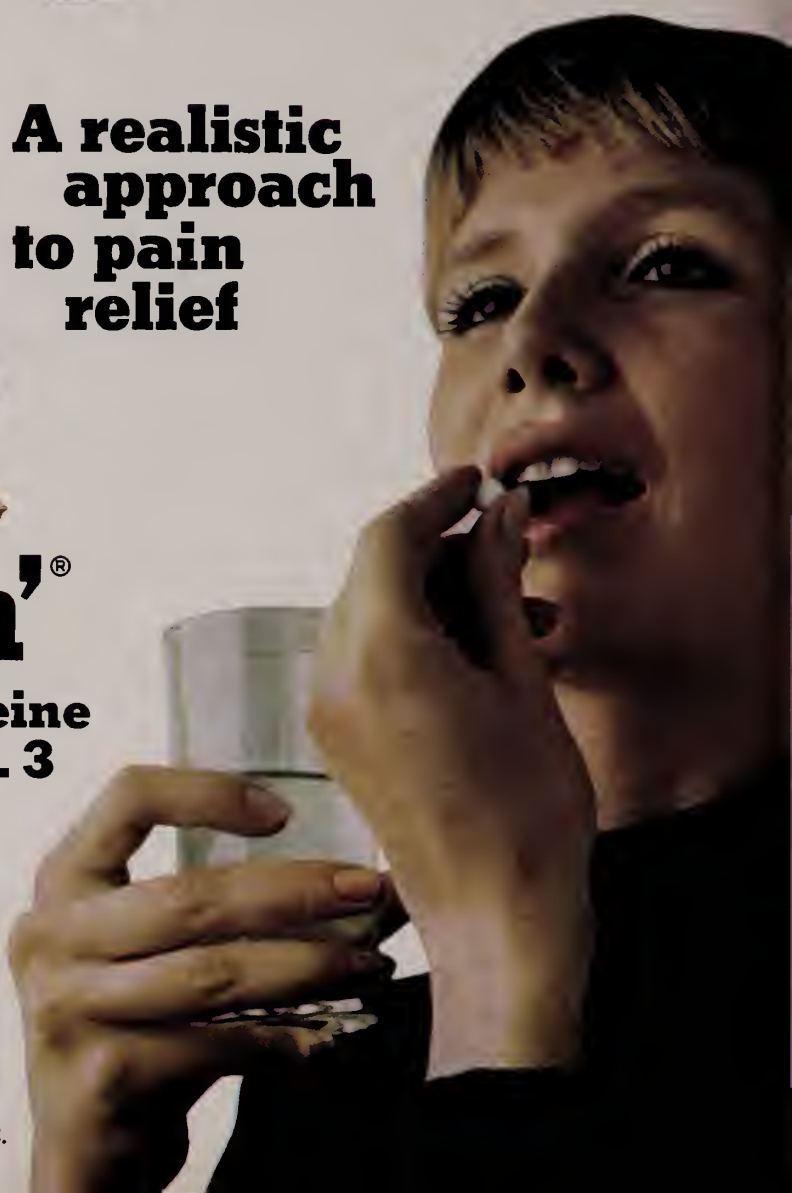


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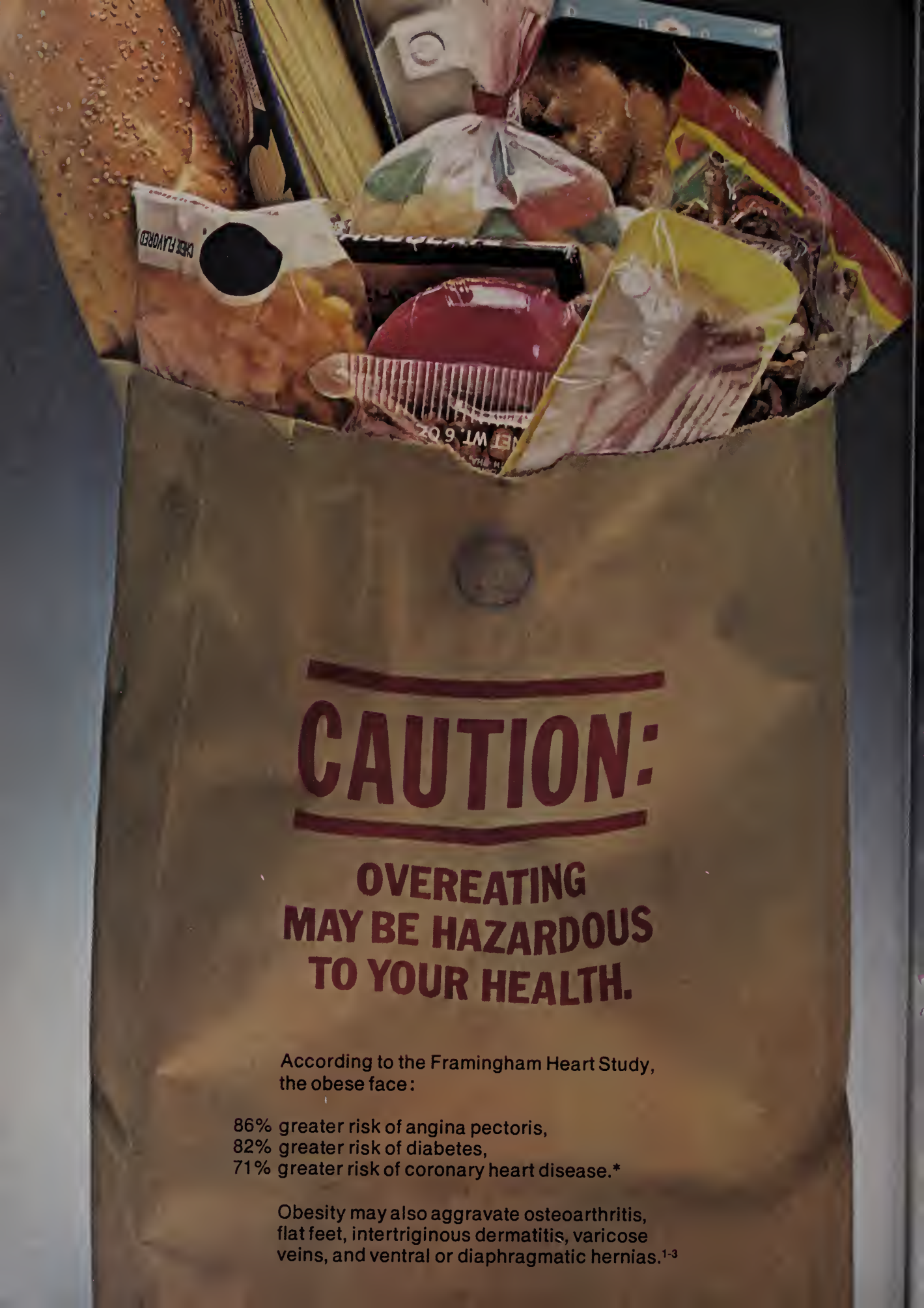
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1. Kannel, W.B., *et al.*: *Circulation* 35:734, 1967.
2. Thomas, H.E., Jr., *et al.*: *Med. Times* 95:1099, 1967.
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Continued to page 464

Otolaryngology Clinics

Nasal Fractures

THE SINGLE MOST common fracture is a fracture of the nose and all physicians who treat emergencies will be faced with the problem of an injured nose. They must decide whether or not there is a fracture of the bone or cartilage and whether any treatment is necessary. Because the nose is not a vital organ, there is a great tendency to neglect injuries, passing them off until too late for early, simple repair.

Control of Bleeding

Epistaxis is an almost universal symptom of nasal injury. Usually it is self-limited. Strips of cotton gauze can be soaked in 4% cocaine and inserted into the nose to hasten cessation of bleeding; cotton pledgets are best avoided for they may be difficult to remove or forgotten. After bleeding stops, the gauze should be removed and the nose examined.

Cartilage Injury

Because cartilaginous injuries require early treatment for best results, all nasal injuries should be examined within the first twenty-four hours. Children, in particular, are susceptible to cartilaginous injuries. Two areas must be examined. The septum is studied for laceration, hematoma, or deflection, and the cartilaginous vault is checked for hematoma. Injuries may tear the upper lateral cartilage from the nasal bone, deforming the cartilaginous vault. The most universally available instrument is the otoscope with a wide nasal tip.

Nasal Bone Injury

As one looks at the edematous ecchymotic external nose, fracture of the nasal bone is obvious if the nose is displaced. The best way to look for displacement is to stand above the patient's head and look down the nose at the chin. Ecchymosis is present in only about half of nasal bony fractures. The best symptom, besides displacement, to suggest a fracture is point tenderness over the nasal bones. There is no substitute for careful digital palpation of the nose and, by gently rubbing the palpating fingers back and forth, edema can often be milked out of the tissue and the nasal bones themselves felt.

Crepitation* is a rare finding; within a few hours after injury, edema occurs to such a degree that crepitation is eliminated. Nasal obstruction is not a reliable symptom of a fracture. Patients with obvious nasal fractures may breathe very well. On the other hand, the nose can be filled with clots. Mucosal lacerations and their accompanying edema may obstruct the nose in the absence of a fracture of either the septum or the bones. In addition to carefully palpating the bony dorsum, one should feel the base of the columella where fractures of the nasal spine can be felt as slight movement. The least finger can be inserted in the nose and the lateral wall palpated. Fractures

*See Test Your Word Score page 415.

in which the nasal process of the maxilla is depressed downward and inward can be detected in this way.

X-ray Findings

While clinical examination is the main way to detect a nasal fracture, x-rays are helpful. They may be important in law suits; they may also show some feature not previously known; e.g., the patient may have had a previous rhinoplasty, and a bony implant may be visible on fracture. Nasal fractures are usually taken in two lateral views and an occlusal view.

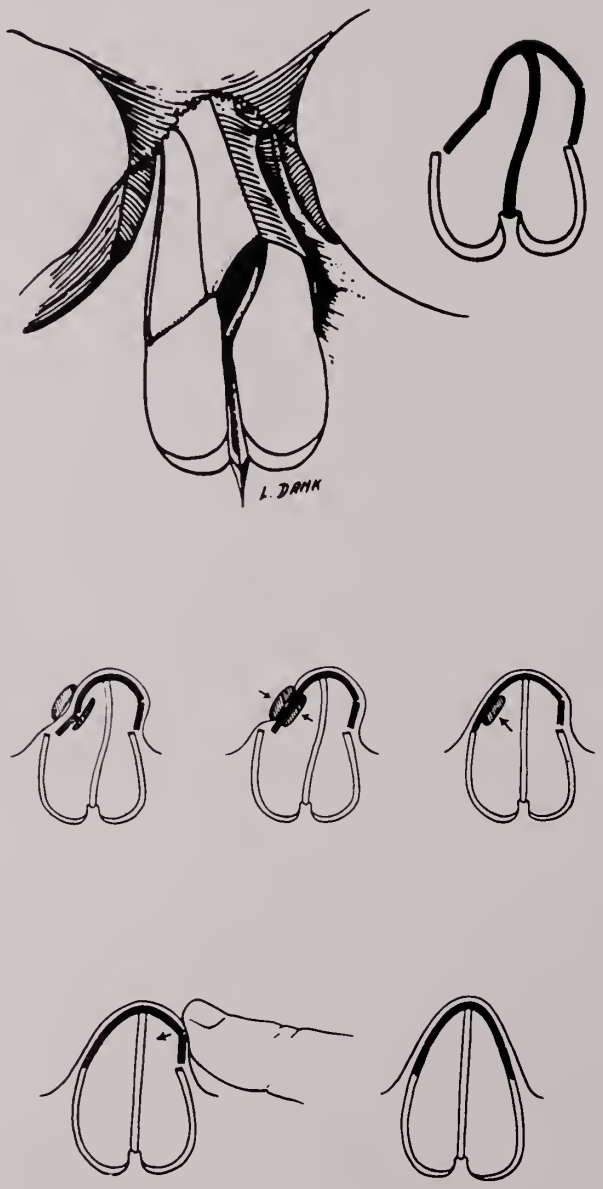


Fig. 1—Diagrammatic representation of lateral fracture demonstrating dislocated naso-maxillary suture and fracture lines and showing in sequence: application of Walsham forceps, closure to reduce dislocation, elevation of depressed side, finger pressure on convex side to reposition, and re-aligned nose (after I. B. Goldman).

Lateral View

In the lateral view the naso-maxillary suture and the linear nasociliary vessels and nerve grooves can be seen. These appear as fine lines on the lateral view; they may be mistaken for fracture lines. The age of fracture lines usually cannot be differentiated on x-rays; old fractures may not have healed to eliminate the lines and may be indistinguishable from recent trauma. Also evident on the lateral x-ray is the nasal spine of the maxilla, which also can be fractured and displaced.

Occlusal Views

Occlusal views are taken to project the nasal bones over the incisor teeth when the film is held in the mouth and the x-ray is shot downward onto the film. Children and some adults have small nasal bones that will not project over the teeth; therefore occlusal views cannot universally be used.

Water's Views

A Water's view of the skull is useful in nasal fractures to rule out any associated zygomatic or maxillary injury.

No Evident Fracture

Nasal x-ray films may be read as "no evident fracture" or as "normal," but this interpretation does not rule out a fracture. Clinical examination is more important than x-rays, and one can have a fracture and a badly displaced nose with the x-rays read as "normal." After a careful initial examination, one may not be able to say definitely whether or not there is a nasal injury, because the nose appears grossly symmetrical but is generally swollen. In this case the patient should be reexamined in three to four days as edema



Fig. 2—Preoperative view.

recedes. Nasal fractures in children can be fixed in five to seven days, and in adults in ten or twelve days with good results. The second examination will reveal bony deviations and chips or projections in the nasal dorsum. Even if there is an obvious fracture, better results can be obtained by allowing some of the edema to diminish. Too early a reduction may give a poor result because the surgeon is not able to palpate carefully and position the nasal fragments.

Treatment

Nasal fractures demand excellent anesthesia and a careful exacting approach best available in the operating room. Everyone is interested in cosmetics when his own nose is involved, and the surgeon should not hesitate to get as good a cosmetic result as possible.

Hematomas

Hematomas of the nasal cartilages must be done in the operating room under sterile conditions to avoid infection. These hematomas do not always look discolored and may give the appearance of the nasal septum being widened and pushed laterally into both nostrils. Treatment of a septal hematoma consists of incision, removal of clots, and insertion of nasal packing into the nostrils to prevent a recurrence. A small drain, like a polyethylene tube #240, may be left in the hematoma itself. Large hematomas of the upper lateral cartilages are also treated by incision and drainage intranasally.

The Lateral Blow Fracture

The most common nasal fracture and one of the most easily treated is that due to a lateral blow. It is really a fracture dislocation with a convex and a concave side. The naso-maxillary suture on the concave side is elastic and is dislocated. This fracture can be handled as the illustrations show after the nose is anesthetized.

In adults, topical 4% cocaine is used on half-inch gauze packing, wrung out and placed in the nose. Injections of Lidocaine 2% with epinephrine 1:100,000 are made in the base of the nasal septum to block nerves of the anterior palatal foramen. The anterior ethmoidal nerve is blocked by injecting as far back and as high on the septum as possible; the infra-orbital nerve, by injecting along the lateral side of the nose; the super-trochlear nerve, by injecting at the root of the nose; the external nasal nerve, by injecting on the nasal dorsum at the junction of the nasal bone and cartilage. If the operation is to be done under general anesthesia, as in children, local anesthesia is still used for its vasoconstricting action.

The naso-maxillary suture is first reduced using a Walsham forceps. Simply closing the forceps with one blade internally and one blade externally reduces the suture. An elevator is then placed in the opposite nostril and the nasal pyramid returned to the midline. As the elevator is lifted upward and over, the nasal bones are molded with the fingers. Usually the nasal septum is not involved in these lateral fracture dislocations. Useful elevators are many: the Boies or Goldman elevators, the No. 7 Bard-Parker handle, or even a thin straight hemostat.

Glancing Blow Fracture

Occasionally a glancing lateral blow will depress a single nasal bone; palpa-

tion of the nasal pyramid will reveal this. Such a depression is a very simple injury to treat; the nasal bone is simply elevated. If it has a tendency to fall back, nasal packing is inserted for four days. Most laterally displaced fractures are amenable to closed reduction using simply elevation. Rarely a fracture may be greensticked, and one must do a lateral osteotomy to complete it. For the general physician failure to achieve the reduction by closed methods should be reason to refer the patient.

Downward Blow Fracture

Downward blows of the nose may, in their simplest form, cause a chipping of the end of the nasal bone. On x-ray one can see that the distal nasal bone is depressed below the level of the rest. If the septum appears intact, these fractures can frequently be treated by simply elevating the nasal bone. Before treatment one can palpate the dorsum carefully and feel a slight step where the bone is down. Fractures of the nasal spine may be ignored unless there is an associated fracture of the septum.

Open Reduction

The most common indication for open reduction of a nasal fracture is the combination of a septal fracture plus a bony fracture. The septum does not lend itself to closed manipulation; this must be treated by open surgical attack. A second indication for surgery is the fractured nose that has had a previous rhinoplasty or septoplasty. The combination of a surgical procedure and recent trauma may have compromised the support of the nose, causing a saddling of the nasal dorsum. Frequently closed reduction alone will restore the profile line, but not always, and complete rhinoplasty, including grafts or implants, may be required. Third, failure to achieve success by closed reduction is an indication for open reduction. This may be because of a green-



Fig. 3—Postoperative view.

stick fracture or because of an unsuspected injury to the septum. Lastly, open reduction is indicated when the patient has suffered a nasal fracture and wants to take this opportunity for a complete re-shaping of the nose. Perhaps he has had a hump and, now that the nose has been injured, wants the entire profile line altered. This can be done; but rhinoplasty at the time of injury is more difficult than a later rhinoplasty done on solid nasal pyramid. In short, all nasal injuries should be suspected of being fractures. Once recognized, most fractures can be treated by manipulation; only a few require open rhinoplastic surgery.

John Banovetz, M.D.
Minneapolis, Minnesota

Reference

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Contributions to Science

In Bernard's discussion of the experimental method in medicine there is one point that seems unacceptable today—his objection to the use of statistics. Since 1865, and especially since the 1920's and 1930's, there has been a great refinement of statistical methods, and it is obvious that medicine has benefited from intelligent applications of statistical theory.

But Bernard's objections were well taken in 1865, even if they are less valid today. He had two principal objections. The most obvious problem was simple foolishness in the use of numerical data and averages. As an example Bernard mentions the scientist who took a sample of urine from a urinal in a railroad station. He analyzed it and announced its composition as being that of "average" European urine. The scientist reasoned that since the urinal was in a railroad station, travelers from all over Europe had an opportunity to use it and it must therefore contain at any given time "average" urine. This particular example might not be repeated today, but there has never been any shortage of foolishness, and there is no reason to believe that other, more plausible idiocies are not being published in medical journals today.

Bernard's other objection is more fundamental. . . . To put it simply, Bernard was afraid that a statistical approach would encourage intellectual laziness and allow researchers to slack off in their efforts to find exact causes in medicine. In Bernard's own words:

"A great surgeon performs operations for stone by a single method; later he makes a statistical summary of deaths and recoveries, and he concludes from these statistics that the mortality law for this operation is two out of five. Well, I say that this ratio means literally nothing scientifically and gives us no certainty in performing the next operation; for we do not know whether the next case will be among the recoveries or the deaths. . . . We must study causes of death with great care and try to discover in them the cause of mortal accidents. Thus, if we accurately know the cause of recovery and the cause of death, we shall always have a recovery in a given case. We cannot, indeed, admit that cases with different endings were identical at every point. In the patient who succumbed, the cause of death was evidently something that was not found in the patient who recovered; this something we must determine and then we can act on the phenomena or recognize and foresee them accurately."*

*Jerome Tarshis: Claude Bernard, Father of Experimental Medicine, 1968.



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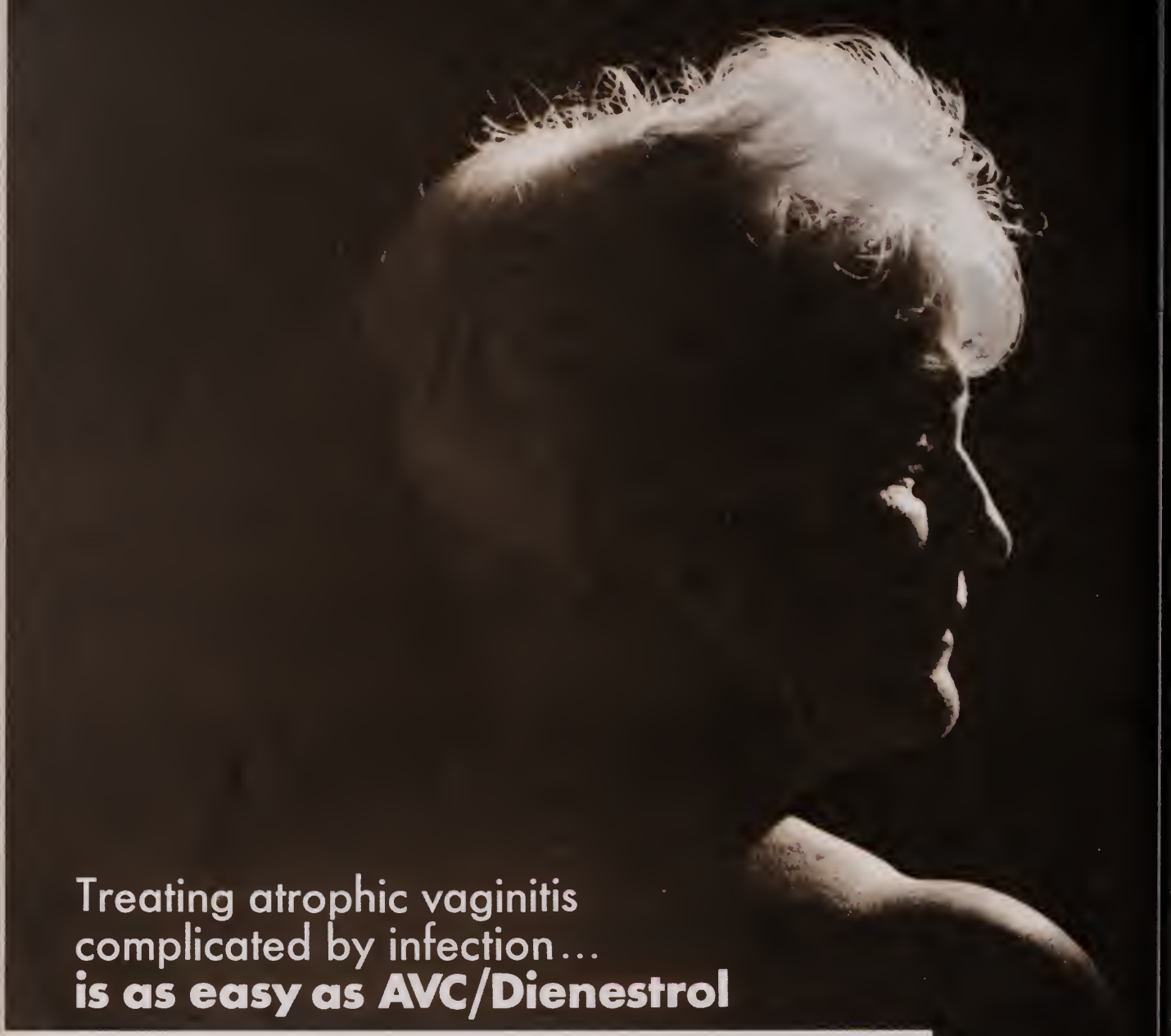
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References: (1) Solerno, L. J.; Ortiz, G., and Turkel, V.: Vaginitis: A Diagnostic and Therapeutic Approach, Scientific Exhibit, presented at the 115th Annual A.M.A. Convention, Chicago, Illinois, June 1966. (2) Nugent, F. B., and Myers, J. E.: Pennsylvania Med. 69:44, 1966.

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Dermatology

Hemangiomas

CARL W. LAYMON, M.D.*
Minneapolis, Minnesota

HEMANGIOMAS MAY be present at birth or appear later. They are circumscribed growths made up of blood vessels.

Types

Nevus Flammeus

Nevus flammeus (port-wine stain) is a capillary hemangioma characterized by nonelevated pink, red, or purple lesions.

Nevus flammeus is frequently unilateral and located on the face and neck, but it may involve large areas of the body. It occurs most frequently in children, may be single or multiple and range from small red macules to large purple patches. The surface is usually smooth; occasional nodular outgrowths may be present. The occurrence of this type of angioma in the nuchal region is common.

Hemangioma Simplex

Hemangioma simplex (strawberry mark) contains dilated capillaries and small veins or arteries and varies in size, ranging in color from red to purple. It is usually raised and sometimes broken up into small components, between which the skin is telangiectatic. The face and neck are the usual locations; but any part of the body may be affected. Ulceration and hemorrhage occur occasionally.

Cavernous Hemangioma

Cavernous hemangioma has larger and more widely dilated vessels with narrow connective tissue septums. It also varies in size and shape, is usually round or oval, and is bright red to deep purple. It has a spongy consistency; if it persists into adult life it may become fibrous. The growths occur on any part of the body; but, as in hemangioma simplex, the head and neck are involved most frequently.

Treatment

Spontaneous involution occurs within the first five or six years of life in many hemangiomas of the strawberry and cavernous types. Hence some physicians believe that if the size and location of the growth and the parents'

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Reprint requests to 538 Southdale Medical Building, Minneapolis, Minnesota.

cooperation justify it, observation rather than active treatment is preferable. Most also believe that if the parents are unwilling to wait for spontaneous involution, the form of treatment considered best should be administered.

Injection

The injection of sclerosing fluids frequently causes ulceration with subsequent scarring; hence it is rarely used.

Carbon Dioxide

In hemangiomas of the strawberry and cavernous types, applications of solid carbon dioxide frequently produce satisfactory results. The carbon dioxide is collected in a bag made of chammy from which it is transferred to molds of various sizes to suit the individual lesion. The molded solid carbon dioxide is then applied with moderate pressure from three to 10 seconds. Swelling and the formation of a bulla followed by erosion and crusting result in most cases. Uneventful healing occurs, however, within a period of two to four weeks, leaving a soft, supple, nonhypertrophic scar, which later fades almost into invisibility. Intervals between treatments are three to four weeks depending upon the degree of local reaction. Prolonged applications (30 to 60 seconds) under firm pressure are not advocated because of the intensity of the reaction.

X-ray and Radium

Most hemangiomas of the cavernous and strawberry types respond to both x-rays and radium. The injudicious use of either of these agents, however, can produce serious or even disastrous sequelae. Such treatment should never be attempted by one who does not understand the details of application of these modalities. The production of radiodermatitis as a result of the treatment of cavernous or strawberry hemangiomas is heartily condemned. Such sequelae persist throughout life and not only lead to disfigurement, but may eventuate in squamous cell carcinoma. Other disastrous results rarely follow the use of ionizing radiation in the treatment of hemangiomas: osseous atrophy, sarcoma arising in irradiated bone, and agenesis* of the female breast.

The hazards of any effective form of treatment of nevus flammeus are great; it is best not to treat it at all. Radium, x-rays, solid carbon dioxide, and other modalities make the lesions worse rather than better in most cases. It is possible to conceal the majority of port-wine stains by cosmetic preparations.

*See Test Your Word Score page 415.

Medicine in Prehistoric Times

In the Neolithic Age there was a great advance in surgical instruments. In addition to sharpened pieces of flint there were now thorns and the teeth of fish and animals. When a surgeon laid out his instruments, preparatory to an operation, the patient usually took a quick look and fainted dead away, making anesthesia unnecessary. However, the anesthetist stood by with a large club in his hand, ready to take care of the patient if he showed signs of life.

"Hand me an incisor; I want to make an incision," a surgeon might say to his nurse. Or "Give me a thorn; I want to see whether the fellow is really unconscious."*

*Richard Armour: It all Started with Hippocrates, 1966.

Alcoholism

An Alcoholic Treatment Center

An Interim Report on the Planning and Implementation within a Community

In the past decade the major national health organizations have officially recognized alcoholism as a treatable medical entity. On this basis, St. Mary's Hospital formed a committee to investigate the possibilities of opening an alcoholic rehabilitation unit within a privately owned and operated general hospital, consisting of two family practitioners, two psychiatrists, two internists, a pathologist and an anesthesiologist.

It became apparent early in the investigation of this committee that a program would include the traditional doctor-nurse relationship, implemented by clinical psychologists, professional counselors, social workers, lay counselors, occupational therapists, recreational therapists, clergymen, and volunteer workers. It was at this point that negotiations were begun with the Johnson Institute, a non-profit community agency which has been functioning for some years as a pre- and post-treatment counseling service for alcoholics and their families.

Treatment Procedure

1. The patient is admitted to the hospital by his own physician who is responsible for all medical treatment while the patient remains in the hospital. This consists of a history and physical examination, any necessary laboratory and x-ray procedures, and consultation with any of the medical specialists on the hospital staff.

2. The program is generally designed to encompass a 21-day stay after detoxification, which is generally accomplished within three or four days after admission by the use of medical regimes and group support. We might state at this point that in the initial planning an intensive care area was deemed necessary. However, our experience has shown that the incorporation of the acutely intoxicated patient into the general ward group is mutually beneficial and actually seems to reduce the time required for detoxification.

3. The patient is given an initial interview by a counselor regarding the length and scope of his drinking history and problems.

4. The patient's family is interviewed during the first days of hospitalization to determine their impressions of the patient, their attitude toward him, and a brief look into their own emotional well-being.

5. The patient receives two hours of group therapy a day, six days a week.

6. During the hospital stay the patient attends at least two additional in-depth counseling sessions.

7. A daily lecture schedule has been devised encompassing the entire field of alcoholism from the patient's point of view. There are 63 lectures in this series, delivered by the medical staff, the counseling staff, and a selected group of clergymen with professional training and experience in the field of alcoholism. Intimates of the alcoholics (spouses, parents, relatives) are encouraged to attend lectures.

8. As the patient nears the end of his hospitalization, his entire family is called in for a lengthy counseling session to try to establish a desirable emotional environment within the family to assist the patient in his recovery after discharge.

9. It has been our experience that a large number of our patients are mixing alcohol and other chemicals—primarily tranquilizers—in their addictive syndrome. This has been particularly true of our female patients. We therefore feel it is vital that the patient be removed from all mood-changing medication as early as possible during treatment. Our experience at this point shows that any patient discharged on mood-changing medication shows a statistically obvious reduction in his maintenance of sobriety.

10. Our experience has shown that a great number of medical problems both related and unrelated to alcoholism are diagnosed and treated during hospitalization: a tremendous advantage to the patient hospitalized for alcoholism in a general hospital where such diagnostic and treatment facilities are available.

11. A program of occupational and recreational therapy is provided to assist the patient in regaining muscle tone and general physical conditioning as well as an excellent opportunity for him to work off anxiety and nervous energy build-up.

12. The final step in hospitalization is a prolonged session with a qualified person, during which the patient reviews his entire life and attitudes toward himself and others as a guideline to readiness for discharge.

13. Upon discharge the patient is informed that he is being transferred from an inpatient to an outpatient status, this latter status to continue for at least two years, during which period he will be required to return to the hospital at least twice a week. These return visits consist of a weekly group therapy session and a weekly A.A. meeting. While he is an outpatient he is assigned an older patient as "sponsor," whose duty is to be responsible for the patient's returning to the hospital for the above meetings. We feel that if we can maintain close contact with the patient during this critical two-year period we can assure him of a statistically accurate and improved chance of life-long sobriety. It is our goal during treatment to halt the progression of the disease; our goal after treatment is to cure the individual from the damage of the disease.

Results

At this time our center has been in operation for sixteen months. During this period we have treated 305 patients. Our recovery statistics are recalculated at the first of each month. As of March 1, 1970, the following are our recovery statistics:

83% of treated patients are now sober and are functioning in our outpatient program. 62% of these people have maintained continuous sobriety since their release from the hospital. 21% of this number have experimented briefly with drinking and have voluntarily returned to the program and are now sober. 17% have returned to their former drinking patterns and are now either actively drinking or under treatment for their disease.

We have recently increased our bed capacity from 16 to 25 beds.

George A. Mann, M.D.*
Minneapolis, Minnesota

*Medical Director, St. Mary's Alcoholic Treatment and Rehabilitation Center, Minneapolis, Minnesota.

Comments

The above-mentioned statistics are, in our opinion, insufficient to draw any far-reaching conclusions. We feel that because of the chronicity of the disease and the high percentage of relapse published by other treatment centers, a two-year period must elapse before meaningful recovery figures can be published. We do, however, feel that because of our close out-patient supervision, such figures when published will have significant statistical accuracy. The national figures for recovery of alcoholics after treatment seem to be in the 50 to 60 percent range.

In addition to treatment of the patient, education and research have been objectives of this unit. At the moment, exploratory talks are being held with the University of Minnesota and the State Junior College system to institute a joint training program utilizing the didactic facilities of the schools and the clinical material available in the hospital to create a training program that would substantially increase the number of trained personnel in our community. At the same time, we are beginning some basic research in areas of clinical investigation and a data-gathering project tied in with other treatment centers in the country by using available computer facilities within the community.

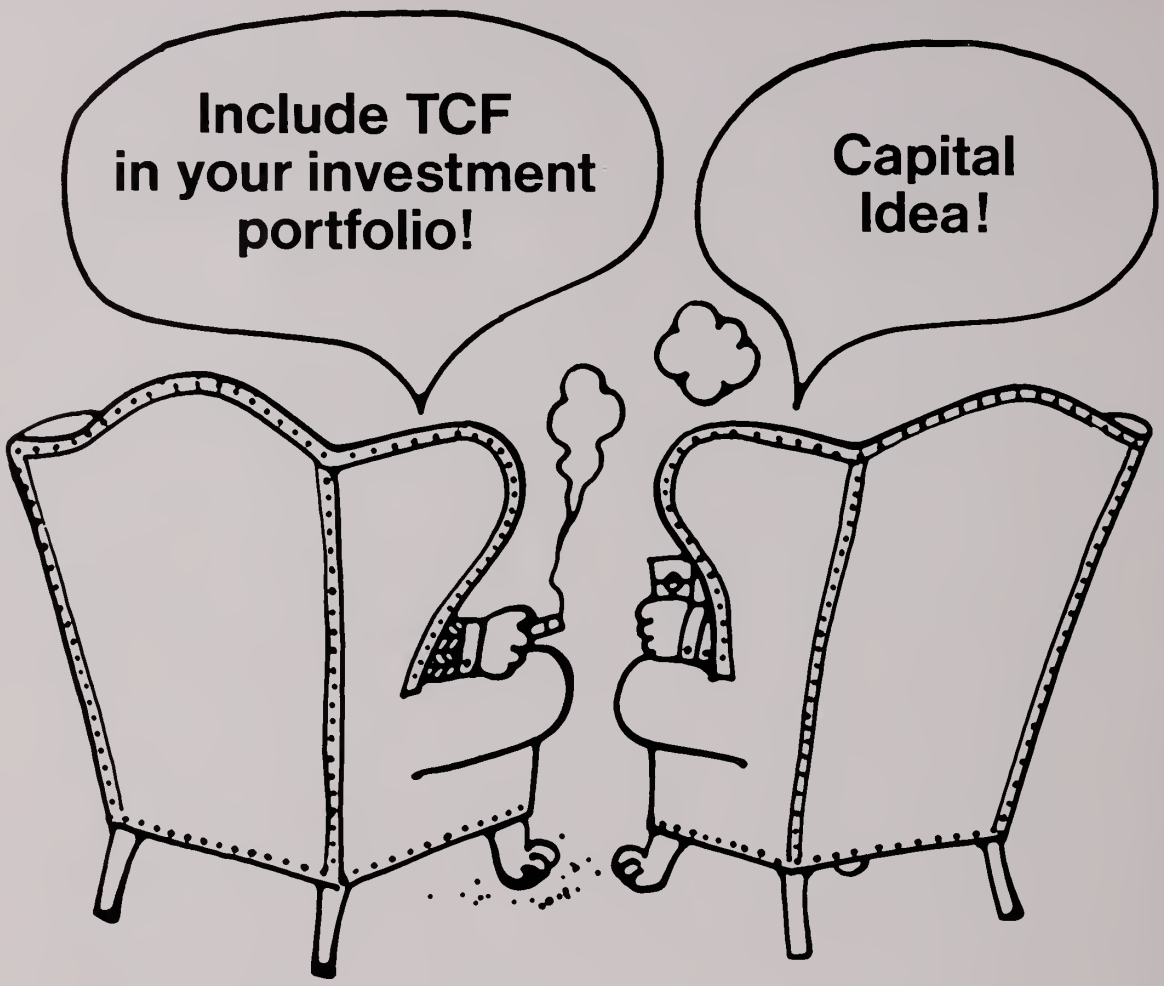
Conclusions

1. It is possible for a private general hospital to function as an effective alcohol treatment and rehabilitation facility.
2. By the joining of already existing community agencies, it is possible to implement the setting up of such a facility and to utilize more effectively the available personnel.
3. Medical, paramedical, clerical, and lay therapists can function effectively as a team within a community hospital.
4. It is possible to weld the alcoholic patient population of such a unit into a tightly-knit, multi-supportive outpatient organization which seems to be extremely beneficial for the on-going sobriety of the patient.
5. The alcoholic patient can be treated within a general hospital without any isolation or restriction of movement and without any disruption of normal hospital routine. Outpatients are allowed almost complete freedom of motion within the confines of the hospital.
6. Because of recent extension by insurance companies to cover such treatment under existing policies, it is economically feasible for such a unit to exist without undue hardship to either the patient or the hospital.

Alcoholism

The immensity of the problem can be realized by considering that persons suffering from chronic alcoholism may no longer be subject to arrest but will have to be treated as individuals suffering from illness. It is estimated that 40 percent of all persons in jails fall into this category. Yet these individuals, great as the number is, reflect only a small portion of the persons suffering from chronic alcoholism.

God brings men into deep waters, not to drown them, but to cleanse them.
—Aughey



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Anesthesiology

Regional Anesthetic Blocks

This is the second in a series of articles reviewing practical regional blocks.

The Ankle Block

The ankle block produces profound anesthesia of the foot and can be used for any operation there. Five nerves must be blocked. Two nerves, the anterior and posterior tibial nerves, are deep and should be blocked specifically by eliciting a paresthesia with the needle. The other three, the superficial peroneal, the saphenous and the sural nerves, are superficial and are blocked by infiltrating a subcutaneous band of anesthetic agent across their paths.

Localizing the Anterior Tibial Nerve

The ankle and foot should be washed and prepared with skin antiseptic and draped with sterile towels so that the foot lies free on the towel.

With the foot pointing straight up, the angle formed by the dorsalis pedis artery and the flexor hallucis longus tendon is located. The anterior tibialis nerve (the deep peroneal nerve) emerges at this point. This nerve should be sought with a sharp, short, 25-gauge needle. When a paresthesia to the first or second toe is produced, 5 cc of local anesthetic agent are injected around (not into) the nerve.

The Long Saphenous Nerve

Using a longer (1½ or 2-inch) needle a subcutaneous band of anesthetic agent is injected medially to the distal end of the malleolus, depositing 6 or 8 cc. This will block the long saphenous nerve which lies anterior to the medial malleolus.

The Superficial Peroneal and Sural Nerves

Another subcutaneous band is then injected laterally from the original wheal all the way to the sole just below the lateral malleolus. This will block first the branches of the superficial peroneal nerve which supplies the lateral part of the dorsum of the foot and finally the sural nerve which lies under the lateral malleolus and supplies the lateral edge of the foot and the heel. For operations on the heel the sural nerve should be blocked where it lies lateral to the Achilles tendon at the same time that the posterior tibial nerve is blocked.

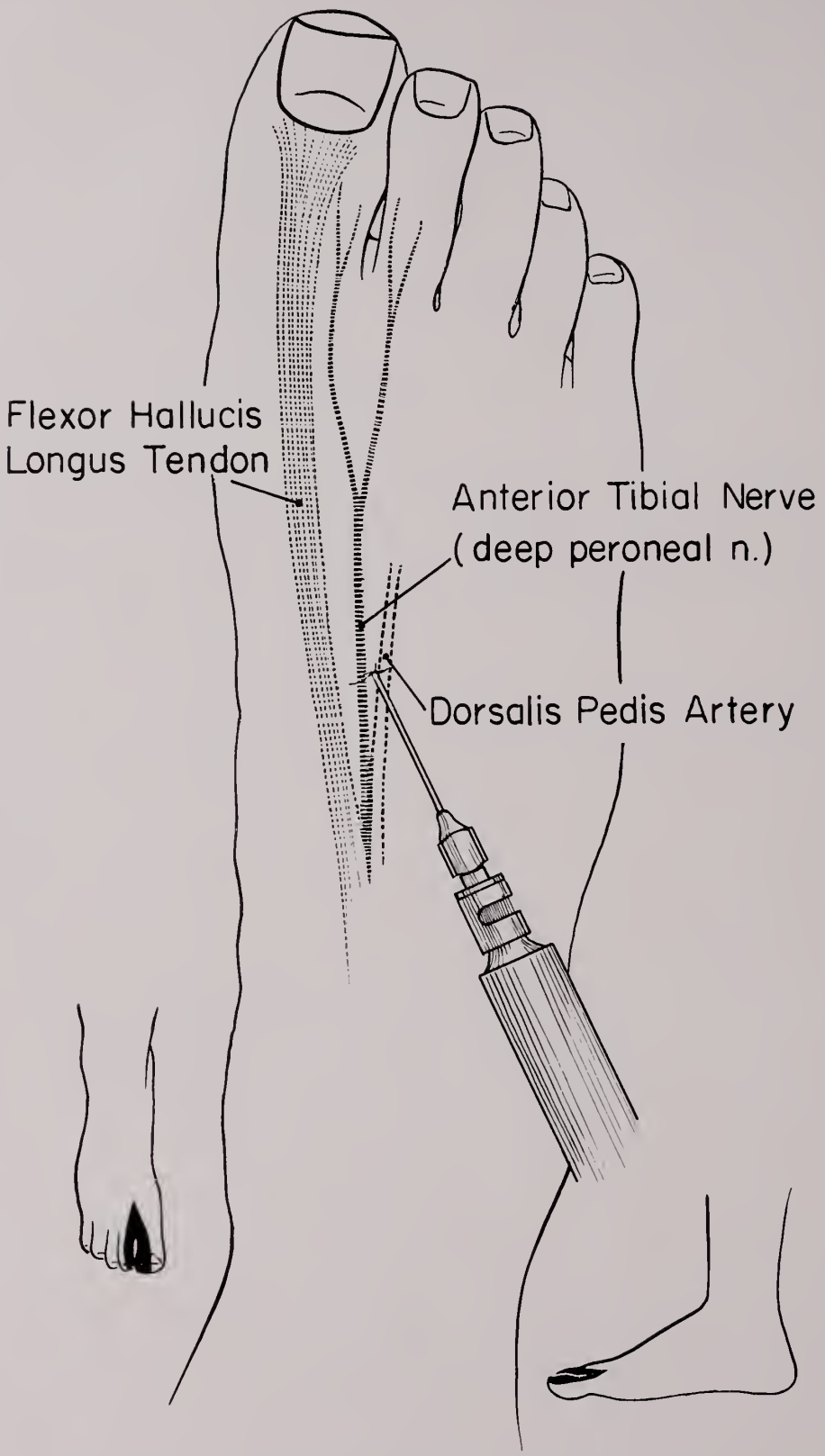


Fig. 1—The anterior tibial nerve is blocked at the angle formed by the flexor hallucis longus tendon and the dorsalis pedis artery. The area of anesthesia produced is represented by the darkened area.

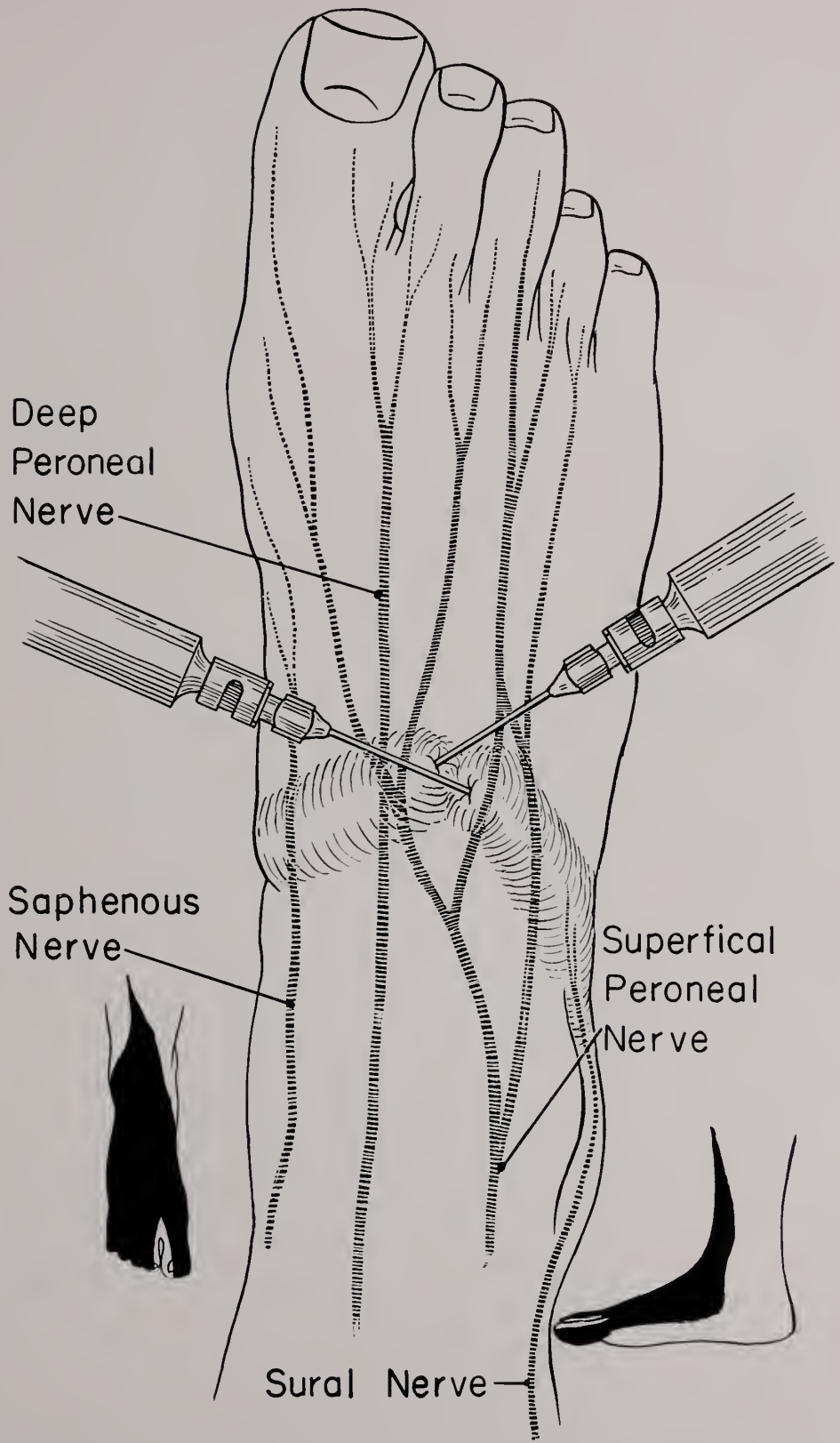


Fig. 2—Subcutanous infiltration to the medial malleolus blocks the saphenous nerve; infiltration to below the lateral malleolus blocks the superficial peroneal and sural nerves. The area of anesthesia produced is represented by the darkened areas.

The Posterior Tibial Nerve

Finally the nerves to the sole of the foot, the posterior tibialis nerve and the sural nerve, if necessary, are blocked.

The best position is obtained by bending the knee and externally rotating the thigh, thereby placing the foot up on the shin of the opposite leg.

A skin wheal is made just medial to the Achilles tendon at the level of the upper part of the medial malleolus. The needle is advanced toward the posterior surface of the tibia and, when a paresthesia to the sole of the foot is produced, 8 cc of anesthetic agent are injected around the nerve.

The Sural Nerve to the Heel

If the surgery involves the sole or side of the heel the sural nerve should

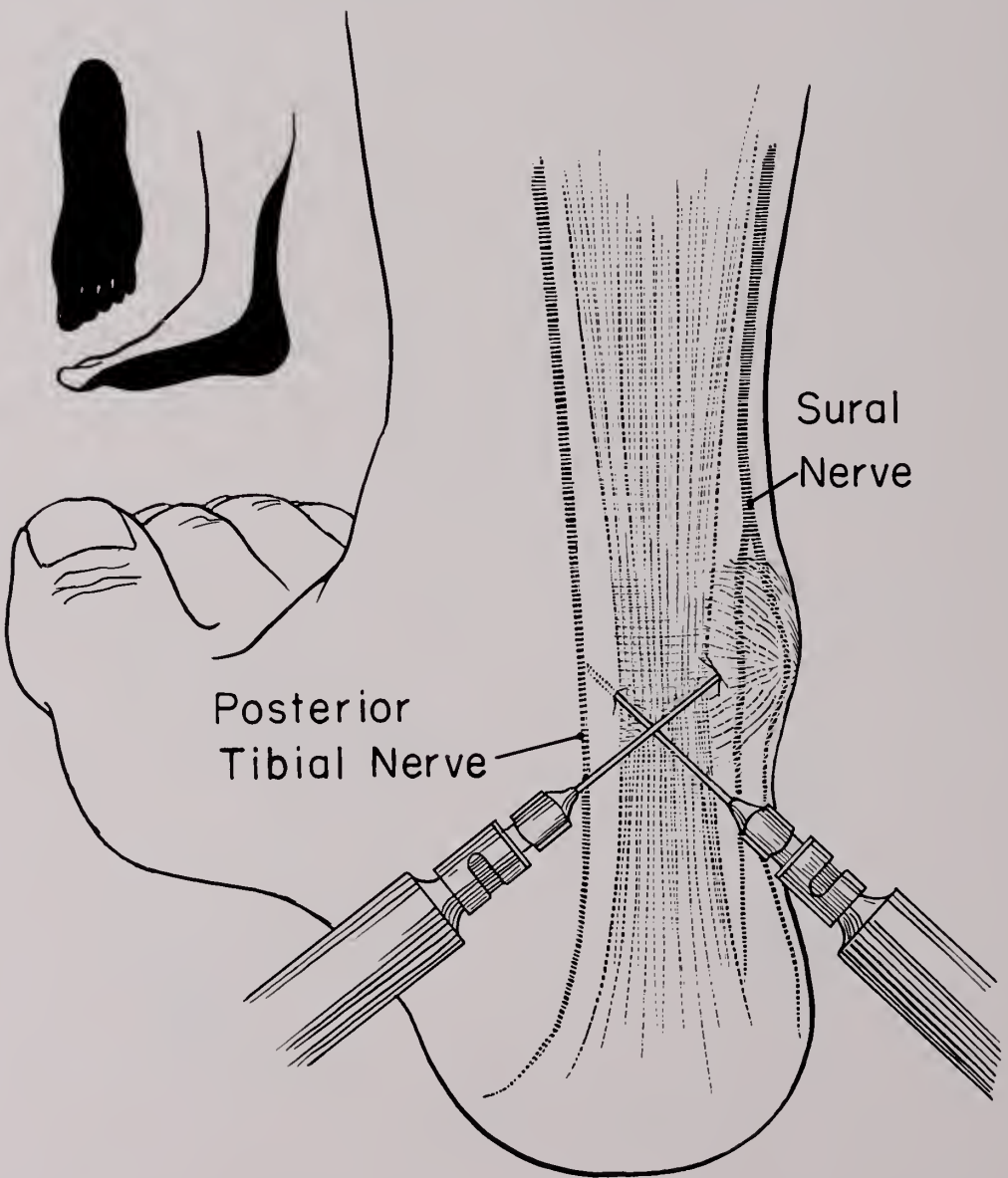


Fig. 3—The posterior tibial nerve lies deep in the space between the Achilles tendon and the posterior surface of the tibia. The sural nerve is blocked by subcutaneous infiltration lateral to the Achilles tendon. The area of anesthesia produced is represented by the darkened areas.

be blocked where it lies lateral to the Achilles tendon. (If only the toes or forefoot are involved, blocking the sural nerve below the lateral malleolus, as described earlier, will be adequate.) To block the sural branches to the heel the needle is inserted into the skin just lateral to the Achilles tendon three inches above its insertion, and then advanced to the lateral malleolus, infiltrating 6 to 8 cc of anesthetic agent into the space between tendon and bone. This will block the many branches of the sural nerve to both sides of the heel, the sole of the heel and the lateral side of the foot.

Eliciting Paresthesia

Eliciting a paresthesia should be done carefully to minimize discomfort to the patient. The operator should warn the patient that he will soon feel "a lightning-like sensation" or "a tingling" in the distribution of the nerve. The patient should be instructed to say "Now" when he feels the paresthesia. Gaining the patient's cooperation is important for success and does not add unduly to his anxiety if one assumes a cool and reassuring manner.

Producing a paresthesia to locate the nerve is not essential to success with this block but is a great help to the beginner who may not be familiar with the exact position of the nerves. After a little practice and some successful blocks this practice can be abandoned. One can usually compensate for some inaccuracy by injecting a larger volume for the same reason that shotguns are preferred to rifles when hunting ducks.

The Anesthetic Agent

Epinephrine should not be added to the anesthetic agent because of the danger of producing ischemia of the toes. For that reason we recommend mepivicaine (Carbocaine) 1% as the agent of choice. However, lidocaine (Xylocaine*) 1%, procaine 2% or tetracaine (Pontocaine*) 0.15% would be satisfactory.

A Tourniquet

A tourniquet can be applied at the ankle where it will be well tolerated and quite effective and will, in fact, enhance the block by preventing loss of anesthetic agent from the foot thereby extending the duration of the anesthetic for as long as the tourniquet can be safely applied.

Van S. Lawrence, M.D.
Minneapolis, Minnesota

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A bore is one who, when you ask him "How are you?" tells you.—Anonymous

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The more I see of men, the more I like dogs.—Madame de Stael

Classified Advertising

Continued from page 444

INTERNIST AND GENERAL PRACTITIONER wanted to join a five-man clinic group in Minneapolis. Complete laboratory and X-ray with board roentgenologist. Excellent hospital staff associations. Salary arrangement to start with, early partnership. Write MINNESOTA MEDICINE—289; 375 Jackson, St. Paul, 55101.

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WANTED LOCUM TENENS: Three-man Minneapolis GP group desires physician with Minnesota license to work parts of the summer and fall of 1970. Salary and conditions excellent. CONTACT 529-9251.

ASSISTANT MEDICAL DIRECTOR—We're looking for a physician under age 40, man or woman, who will appreciate working in a pleasant environment and one of the best locations in the nation to raise a family. We prefer at least two years of private practice; may be internist, surgeon, psychiatrist or general practitioner. This career position on our medical team includes good hours and liberal vacation and benefit program. Salary is negotiable. If interested write to our Medical Director: Fred Dinkler, M.D., The Bankers Life, 711 High Street, Des Moines, Iowa 50307.

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Continued to page 468

117th Annual Meeting
Minnesota State Medical Association

Duluth, Minnesota

May 18, 19, 20, 1970

DISCOVER DULUTH in '70 is the call to all physicians to attend the 117th Annual Meeting of the Minnesota State Medical Association May 18, 19 and 20.

Located at the head of the Great Lakes at the gate of the arrowhead country, Duluth offers a unique setting for our 1970 Annual Meeting in the heart of an area which abounds in points of historical and scenic interest.

The spacious new Duluth Auditorium, located on the shore of Lake Superior, will be the focal point for major Annual Meeting events, including scientific and workshop sessions, noon luncheons, and scientific and technical exhibits.

Traditionally known as the upper midwest's great medical meeting, this year's event will be no exception. The Committee on Scientific Assembly has spared no effort in arranging for an outstanding program which will interest physicians in every medical specialty.

The popular workshop concept initiated at the 1969 meeting will again be featured on this year's program. A series of afternoon workshops will be held Monday, May 18, and Tuesday, May 19. Each workshop will be repeated twice —in sessions lasting from 2:00 to 3:00 p.m. and 3:45 to 4:45 p.m. This arrangement will make it possible for physicians to attend the workshops of their preference with a minimum amount of conflict.

"Massively Injured Patient," "Radiological Workshop," "Exercise for Coronary Disease—When, Where & How," "Reading & Learning Disorders in Children," "Contraceptives," "Antibiotics," "Suction Completion of Abortion," "Office Neurology—Diagnosis and Treatment," are the subjects selected by the Committee on Scientific Assembly for the opening round of workshops on Monday, May 18.

The Tuesday schedule of workshops is equally impressive, and includes the following presentations: "Facial Injuries," "Unconscious Patient," "Office ENT," "Erythroblastosis," "Immunizations," "Arrhythmias, Blocks and Pacemakers," "Treatment of Angina Pectoris," and "Infants with Heart Disease."

The opening scientific session, scheduled for Monday, May 18, at 9:00 a.m., will be devoted to an "in depth" evaluation of the various aspects of "Calcium Metabolism." "What's New in Heart Disease" will be the theme of the "in depth" session scheduled for Tuesday and Wednesday mornings. The "Heart Sessions" have been arranged and sponsored in cooperation with the Minnesota Heart Association.

The Tuesday morning schedule of heart topics will open at 9:00 a.m. with a presentation of "Office Diagnosis of Congenital Heart Disease." Other aspects of heart disease scheduled for consideration Tuesday morning include the following: "Coronary Arteriography, Diagnosis and Treatment," "Diagnosis and Treatment of Pulmonary Embolic Disease," "Rehabilitation after Myocardial Infarction" and "Medical Treatment of Arrhythmias."

Wednesday's heart sessions will begin at 9:00 a.m. with a presentation devoted to "Diagnosis and Treatment of Common Hyperlipidemias." Subsequent topics are "Modern Treatment of Heart Failure," "Diagnosis and Current Treatment of Stroke," "Pericarditis," and "Treatment of Bacterial Endocarditis."

Noon luncheon meetings have been scheduled for Monday and Tuesday. The challenging subject "Communication: Physician-Patient—Physician-Spouse—Who Needs It?!" will be the luncheon theme for Monday. "Newer Approaches to Medical Education" is the topic for the Tuesday luncheon.

The Annual Banquet will be held Monday evening at 7:00 p.m.

The House of Delegates will convene Sunday, May 17, at 2:00 p.m. in the ballroom of Hotel Duluth. Reference committees will meet Sunday evening at 7:30 p.m. and the House will re-convene Tuesday at 7:00 p.m.

Scientific and technical exhibits will be located in the Duluth Auditorium, and all physicians are urged by the Committee on Scientific Assembly to visit the technical exhibits and extend their appreciation to the representatives of the firms who have supported the meeting by their presence.

The Woman's Auxiliary will meet in Duluth in conjunction with the Annual Meeting of the Minnesota State Medical Association.

Pre-registration by physicians is encouraged. To facilitate pre-registration, materials and program information will be enclosed with forthcoming issues of the Newspage and the official program. By completing and returning pre-registration materials to this office, physicians may be certain that their badges will be waiting for them at the Advance Registration Desk in the Duluth Auditorium.

117th Annual Meeting Time Table

SUNDAY, May 17

2:00 p.m.	*House of Delegates* (1st session)	Hotel Duluth
7:30 p.m.	*Reference Committee Meetings*	

MONDAY, May 18

9:00 a.m. to 12:00 noon	"DISORDERS OF CALCIUM METABOLISM"	
	(Intermission to visit scientific and technical exhibits—10:30 a.m.-11:00 a.m.)	
12:30	LUNCHEON	Duluth Auditorium
	Dr. James F. Martin, Minneapolis Consulting Psychologist "COMMUNICATION: Physician-Patient Physician-Spouse WHO NEEDS IT?!"	

2:00 to 3:00 and 3:45 to 4:45 MONDAY WORKSHOPS

1. "Massively Injured Patient"	John F. Perry, Jr., St. Paul, moderator
2. "Radiological Workshop"	Albert I. Balmer, Duluth
3. "Exercise for Coronary Disease —When, Where & How"	Charles R. Jorgensen, Minneapolis
4. "Reading & Learning Disorders in Children"	James F. Mellinger, Rochester
5. "Contraceptives"	William B. Stromme, Minneapolis, moderator
6. "Antibiotics"	Allan C. Kind, Minneapolis
7. "Suction Completion of Abortion"	Joseph H. Pratt, Jr., Rochester
8. "Office Neurology—Diagnosis and Treatment"	Lawrence A. Farber. Minneapolis

3:00 to 3:45 INTERMISSION—To visit scientific and technical exhibits
3:45 to 4:45 REPEAT OF WORKSHOPS
6:00 p.m. PRESIDENT'S RECEPTION
7:00 p.m. ANNUAL BANQUET—New members and wives to be guests of the Association

TUESDAY, MAY 19

9:00-12:00 WHAT'S NEW IN HEART DISEASE?
John G. Fee, Presiding
(Morning program arranged in cooperation with Minnesota Heart Association)

9:00 *Office Diagnosis of Congenital Heart Disease*
Russell V. Lucas, Minneapolis

9:30 *Coronary Arteriography, Diagnosis and Treatment*
George G. Rowe, Madison, Wisconsin

10:00 *Diagnosis and Treatment of Pulmonary Embolic Disease*
Arthur A. Sasahara, West Roxbury, Massachusetts

10:30-11:00 *Intermission*—To visit scientific and technical exhibits

11:00 Rehabilitation after Myocardial Infarction
Herbert A. Schoening, Minneapolis

11:25 *Medical Treatment of Arrhythmias*
T. Paul B. O'Donovan, Rochester

* * * * * * * *

12:30 LUNCHEON — Duluth Auditorium
Richard V. Ebert, Minneapolis
"Newer Approaches to Medical Education"

2:00 to 3:00 WORKSHOPS

1. "Facial Injuries" — Jerome A. Hilger, St. Paul
2. "Unconscious Patient" — Joe R. Brown, Rochester
3. "Office ENT" — Michael M. Paparella, Minneapolis
4. "Erythroblastosis" — Martha J. B. Strickland, Minneapolis; Herbert F. Polesky, Minneapolis; Edward A. Banner, Rochester
5. "Immunizations" — Henry H. Reed, Duluth, and Jerome E. Kwako, Duluth
6. "Arrhythmias, Blocks and Pacemakers" — Naip Tuna, Minneapolis, and Gerald T. Gau, Rochester
7. "Treatment of Angina Pectoris" — George G. Rowe, Madison, Wisconsin, and Gordon K. Danielson, Rochester
8. "Infants with Heart Disease" — James H. Moller, Minneapolis, and Aldo R. Castaneda, Minneapolis

3:00- 3:45 *Intermission*—To visit scientific and technical exhibits
3:45- 4:45 REPEAT OF WORKSHOPS
7:00 HOUSE OF DELEGATES—Second session

WEDNESDAY, May 20

9:00 to 12:00 WHAT'S NEW IN HEART DISEASE (Continued)
James N. Karnegis, Presiding
(Program arranged in cooperation with Minnesota Heart Association)

9:00 *Diagnosis and Treatment of Common Hyperlipidemias*
Kenneth G. Berge, Rochester

9:30 *Modern Treatment of Heart Failure*
Yang Wang, Minneapolis

10:00 *Diagnosis and Current Treatment of Stroke*
Joseph A. Resch, Minneapolis

10:30-11:00 *Intermission*—To visit scientific and technical exhibits

11:00 *Pericarditis*
Howard B. Burchell, Minneapolis

11:30 *Treatment of Bacterial Endocarditis*
Wesley W. Spink, Minneapolis

* * * * * * * *

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Continued from page 464

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PLAINVIEW needs a General Practitioner. Community thirty miles from Rochester and has own clinic and nursing home facilities. Country Club with swimming pool and excellent greens. Contact Dr. Quirim, DDS, Plainview, Minnesota 55964.

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Dial Access Medical Library
New Tapes by Minnesota Physicians

#317: *Treatment of Atrial Dysrhythmias Following Acute Myocardial Infarction*
By Edward A. Ryan, M.D., Duluth

#318: *Heart Block and Pacemakers*
By James I. Thompson, M.D., Duluth

#319: *Treatment of Stasis Ulcers*
By B. F. Fuller, M.D., University of Minnesota

#320: *A Diagnostic Approach to the Patient with Chronic Leg Ulcers*
By B. F. Fuller, M.D., University of Minnesota

#328: *Treatment of Multiple Myeloma*
By Robert A. Kyle, M.D., Mayo Clinic

#329: *Risk Factors in Coronary Atherosclerosis*
By Kenneth G. Berge, M.D., Mayo Clinic

#330: *Preoperative and Postoperative Management of the Hypertensive Patient*
By Philip J. Osmundson, M.D., Mayo Clinic

#331: *Diuretics—Old and New*
By Ross M. Tucker, M.D., Mayo Clinic

#332: *Echoencephalography in the Diagnosis of Cerebral Lesions*
By Burton Sandok, M.D., Mayo Clinic

#333: *Temporal Arteritis*
By John W. Joyce, M.D., Mayo Clinic

#334: *Digitalis Toxicity, Diagnosis and Treatment*
By T. L. Johnson, M.D., Duluth

Vasectomy
By Robert Benjamin, M.D., St. Louis Park Medical Center

Automobile Crash Injuries of the Larynx and Trachea
By David J. Buran, M.D., St. Louis Park Medical Center

Meeting

Minnesota Psychiatric Society annual scientific meeting for members only on April 18, 1970, at the Sheraton-Ritz Hotel, with a dinner-dance to follow. A special feature will be the awarding of the Society's "Mental Health Achievement Award," for the first time, given to any deserving person in recognition of outstanding work in the service of mental health in Minnesota.

Laboratory Letter

A Short But Sweet Account of a Glucose Tolerance Test

"Dear Sir, be short but sweet."
John Fletcher
The Scornful Lady II.ii

THE COMMITTEE on Statistics of the American Diabetes Association recommends the standardized oral glucose tolerance test,[1] and we would like to lend our support.

Preparing Patients

Instruct patients to ingest at least 150 grams of carbohydrate for three days before the test. This should not be hard since the average American diet is 150 to 200 grams of carbohydrate anyway. If the patient has an acute disease, the test should not be done until two weeks after he (or she) has recovered. For at least three days before the test, patients should discontinue drugs known to influence the tolerance test. These include hormones, oral contraceptives, salicylates, nicotinic acid, diuretic agents and, of course, hypoglycemic drugs. Patients should fast at least eight and not more than 16 hours before the test, and during this period should avoid coffee, smoking, and undue physical exertion. Bed rest, particularly in older patients, decreases glucose tolerance. Therefore, glucose tolerance tests should be performed only on ambulatory persons, not on hospital patients confined to bed.

Doing the Test

I will not go into detail here but will hit the high spots. Patients should swallow 40 grams of glucose per square meter of body surface. The glucose solution is not as hard to prepare as it sounds. Given the patient's weight and height, you read off a chart* the grams of glucose to be given, then dissolve this amount in 300 ml. of flavored ice water. Or, if you wish, you may use a proportional number of milliliters of a commercial glucose solution. You draw a fasting specimen, and subsequent samples at one, two, and three hours after glucose ingestion. During this time the patient should remain quiet, subdue his emotions, and refrain from smoking or drinking coffee.

The test ought to be done by one of the following methods: glucose oxidase, Nelson-Somogyi, or the AutoAnalyzer ferricyanide technique. We use the recommended AutoAnalyzer method.

Interpreting Results

Now for the sweet part of this account. Interpreting a standardized glucose tolerance test is sweet because it's simple. The Association suggests a point method to separate the "diabetics" from the "nondiabetics". This is how it works.

Time	mg./100 ml.	Points
Fasting	130 or more	1
One hour	195 or more	½
Two hours	140 or more	½
Three hours	130 or more	1

Two points or more indicate diabetes mellitus. Also, if the sum of fasting, one, two, and three-hour values is 600 or more, the patient is a "diabetic."

Richard L. Reece, M.D.
Minneapolis, Minnesota

*If you desire a copy of this chart, write the author.

Reference

1. Standardization of the Oral Glucose Tolerance Test, Report of the Committee on Statistics of the American Diabetes Association. Diabetes, 18:299, 1969.

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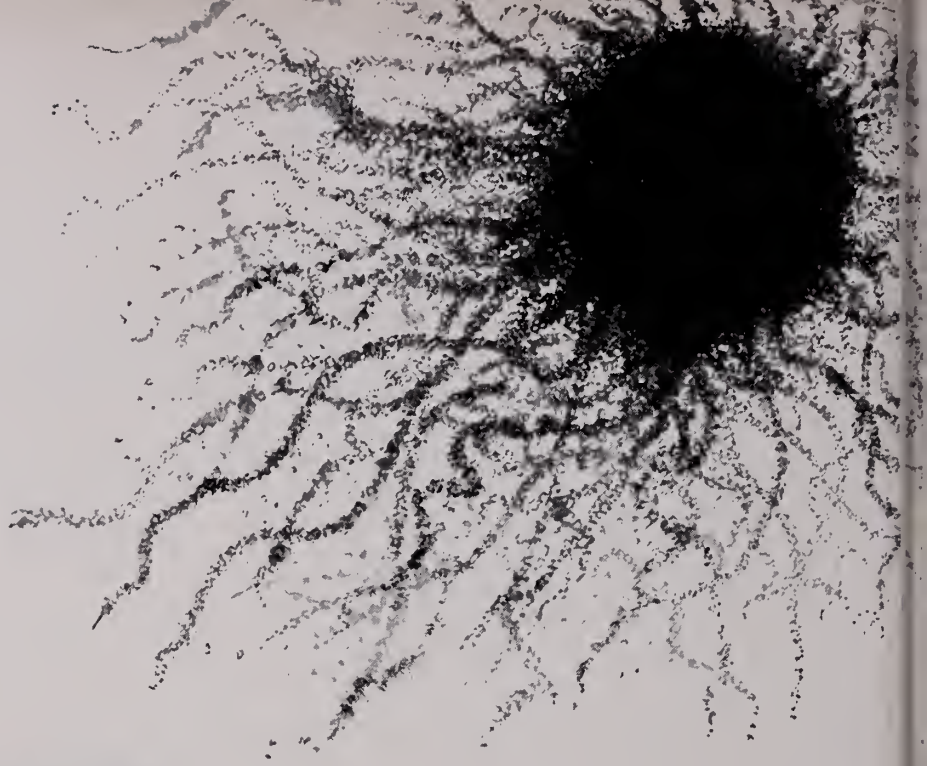
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Precautions: Overgrowth of nonsusceptible organisms may occur. Constant observation is essential. If new infections appear, appropriate measures should be taken. In infants, increased intracranial pressure with bulging fontanels has been observed. All signs and symptoms have disappeared rapidly upon cessation of treatment.

Side Effects: Gastrointestinal system—anorexia, nausea, vomiting, diarrhea, stomatitis, glossitis, enterocolitis, pruritus ani. Skin—maculopapular and erythematous rashes; a rare case of exfoliative dermatitis has been reported. Photosensitivity; onycholysis and discoloration of the nails (rare). Kidney—rise in BUN, apparently dose-related. Transient, reversible, nephrogenic diabetes insipidus with excessive thirst and polyuria (rare). Hypersensitivity reactions—urticaria, angioneurotic edema, anaphylaxis. Teeth—dental staining (yellow-brown) in children of mothers given this drug during the latter half of pregnancy, and in children given the drug during the neonatal period, infancy and early childhood. Enamel hypoplasia has been seen in a few children. If adverse reaction or idiosyncrasy occurs, discontinue medication and institute appropriate therapy. Demethylchlortetracycline may form a stable calcium complex in any bone-forming tissue with no serious harmful effects reported thus far in humans.

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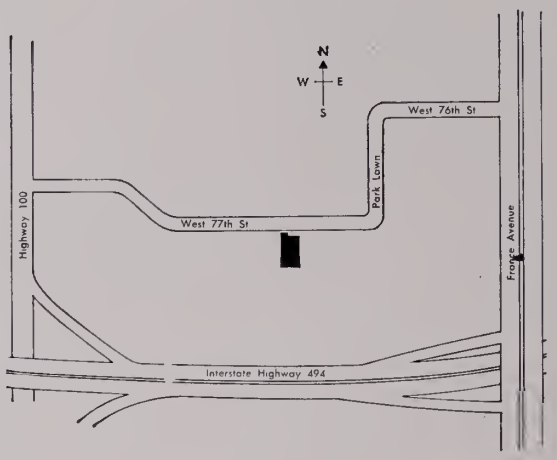
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President's Letter

THE MOST SERIOUS problem facing the medical profession today, as I see it through the eyes of a soon to be Past-President, is the apparent inevitable regimentation of the medical profession by the slow but inexorable encroachment of government. Compulsory health insurance, fixed fee schedules, control of methods of practice, various panel type practices, as well as possible bureaucratic utilization review committees can conceivably be thrust upon us sooner than one may think.

If you are concerned about this problem and I believe all physicians should be, you must take an active part in community political life, medical political action as well as develop an evangelistic attitude, spreading the gospel of a free medical society.

I have had the opportunity this year to attend at least one of the meetings of most of the sixty-two committees which do the spade work for our Association. I am extremely impressed by the energies and concern that the chairman and each member put into the workings of their committees. It is because of the energetic and faithful service of these physicians, that our Association is able to get its work done. Without these devoted people we might be at a standstill. I therefore wish to congratulate the chairmen and the members of each committee for their faithful and dedicated service to our association.

I wish to thank the members of the Council and especially Dr. George Sather, Chairman, for their counsel and guidance during the past year, as well as the Officers and Delegates who have been most kind and helpful.

I wish to thank Dr. Carl O. Rice, Editor of MINNESOTA MEDICINE and Miss Elaine Nye for their advice and help.

It is with pleasure that I acknowledge my deep gratitude to our Executive Secretary, Mr. Harold W. Brunn, and his staff for their suggestions and help. Lastly I appreciate greatly the support all physicians of our Association have given me during this year as your President.

And now the time has come for the "Changing of the Guard." Your new President, Dr. Raymond J. Jackman is most capable and qualified. I have assured him that you will support him as you did me.

Delmar R. Gillespie, M.D.
President
Minnesota State Medical Association

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Number 5

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Lumbar Sympathectomy for Arteriosclerosis Obliterans*

JAMES J. MONGÈ, M.D., M.S.
ROBERT H. LaBREE, M.D.
Duluth, Minnesota

OBJECTIVE MEASUREMENT by digital plethysmography* of the hemodynamic response to lumbar sympathectomy has shown improvement in only one parameter, skin blood flow.[1,2,3,4] Despite this, many clinicians[5,6,7] consider sympathectomy beneficial to the patient with ischemic symptoms due to arteriosclerosis obliterans; others[8,9,10,11] have questioned its value. This analysis of our own patients who underwent lumbar sympathectomy was undertaken to determine how much relief they obtained following surgery and to help select those patients more apt to benefit by the operation.

Clinical Material

The study group was limited to the 132 patients, 96 males and 36 females who between 1950 and 1966 underwent lumbar sympathectomy for the treatment of leg symptoms due to arteriosclerosis obliterans. Since reconstructive procedures were not available in the early years or, in later years, were thought inadvisable because of occluded distal vessels, none of these patients had undergone angioplastic surgery. Both the clinic charts and the hospital records were perused, and follow-up information was obtained either by re-examining the patient or by specifically inquiring about his condition by letter. A total of 181 lumbar sympathectomies were performed (bilateral sympathectomies for 40 males and nine females). The second through the fourth lumbar ganglia and the intervening sympathetic trunk were removed in every case. When the patients undergoing unilateral sympathectomy were tabulated, 67 percent of the men had had the left side operated ($P = < 0.01$) and 67 percent of the women had had the right side operated ($P = < 0.05$). No explanation could be found for this difference.

Age

For both sexes the age range was 37 to 78

*See editorial page 517.
†See Test Your Word Score, page 523.

years. The average ages were almost the same, 59 years for males and 60 for females. Four women were still menstruating.

Diabetics

Diabetes mellitus was present in 26 percent of the men and 39 percent of the women; the mean age for the 39 diabetic patients was 1.5 years older than for the non-diabetics. Thirty-six percent of the men and 44 percent of the women had hypertension; 20 percent had sustained a myocardial infarction, and 13 percent had had a cerebrovascular accident. Half of these patients had had their heart attack or their stroke prior to surgery (Table 1).

TABLE 1

Patients Undergoing Sympathectomy for Arteriosclerosis Obliterans

Medical Data

Diabetic	—Males —25	Cigarette Smoker	—106 pts
	—Females—14	(Heavy Smoker)	— 36 pts
Hypertensive			
	—Males —35	Non-smoker	— 17 pts
	—Females—16	Unknown	— 9 pts
Obese	—17 pts		
Myocardial Infarction	—25%	Cerebrovascular Accident	— 13%
Prior to surgery	—14 pts	Prior to surgery	— 8 pts
After surgery	—20 pts	After surgery	— 9 pts

Medical Data. Medical data obtained from the preoperative evaluation of the patients as well as from follow-up information.

Tobacco

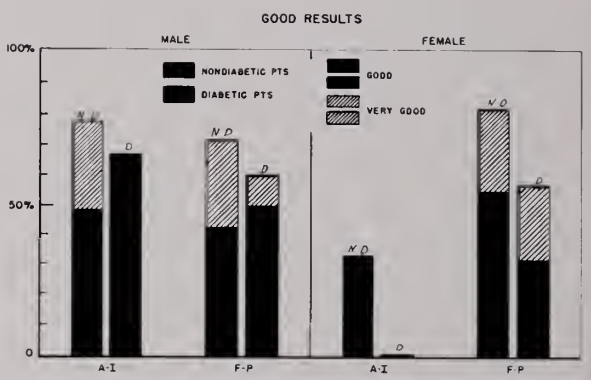
Cigarette smoking was a common habit in these patients. While the information is not complete, 80 percent were known to smoke and 13 percent were known to be non-smokers. One third of the smokers used more than one pack of cigarettes a day. Only four men and three women neither smoked nor had diabetes mellitus; in these seven patients ischemic symptoms were milder and of less serious consequence. Fourteen patients discontinued smoking after sympathectomy, although all were urged to do so.

Results

There were no postoperative deaths. Morbidity was limited to a few patients with postoperative ileus, and a sizeable number (30 percent) with post-sympathectomy neuralgia. Patients without open ulcers were ready for hospital discharge five to seven days after surgery.

Improvement

Over-all improvement occurred in 70 percent of the affected limbs and 73 percent of the patients (Figure 1). Although 80 percent who underwent bilateral sympathectomy obtained benefit, this somewhat better result is explained by selection. Half of these patients, having had one leg helped by sympathectomy, subsequently had the contralateral lumbar sympathetic trunk removed when distress developed in the other leg.



AI—Aortoiliac Occlusion FP—Femoropopliteal Occlusion
The outlined bar signifies the per cent of patients in each group who had good results.

Fig. 1—Good Results. The percentages of good results for the patients are listed according to the level of occlusion, aortoiliac or femoropopliteal, sex and the presence or absence of diabetes mellitus. The very good results are distinguished by the diagonally lined portion of the bar and good results by the solid portion. (There were no diabetic females with aortoiliac occlusion.)

Skin Temperature

In 26 of the patients either the skin temperature increased after a nerve block or perspiration occurred over the legs and feet after warming. A good result was achieved in 85 percent of these as compared to 66 percent of the other 106 cases ($P = < 0.05$). Patients complained, often bitterly, of post-sympathectomy neuralgia involving the anterior thigh. The pain began on about the 12th postoperative day and lasted for four to six weeks. On questioning it was found that 89 percent had gained relief of their symptoms after operation, a significantly greater incidence than that for the rest of the group ($P = < 0.01$).

Arteriograms

Arteriograms were still available for 40 patients. Six had aortoiliac and 34 femoropopliteal occlusion. These films were reviewed to ascertain the degree of patency of the distal popliteal, the peroneal, the anterior tibial, and the posterior tibial arteries. Each vessel was graded from zero for complete occlusion to four if there was no obstruction (Table 2).

TABLE 2
Patients Undergoing Sympathectomy for Arteriosclerosis Obliterans

Correlation of Results with Popliteal Outflow

	Popliteal Artery Outflow			
Results	0-3	0-6	7-11	12-16
Excellent	3**	0	2	1
Good	3	2*	12*** **	3*
Poor	1*	2*	2*	1
Amputation	5*	1*	1*	1*

—signifies the number of diabetic patients.

Correlation of Results with Popliteal Outflow. Grading of the degree of distal outflow obstruction shown on the arteriograms. (After the method of Morton et al.[12]) The distal popliteal, peroneal, anterior tibial and posterior tibial arteries were graded from 0 for complete obstruction to 4 if the vessel was entirely patent, and the four grades were totaled.

Morton et al.,[12] who first proposed this method, found that the severity of patients' symptoms and the results of femoropopliteal endarterectomy could be related to the degree of outflow obstruction. In our study most of the cases which required amputation had a high degree of occlusion of the vessels of the popliteal trifurcation and a score of zero or one. The three patients with a score greater than one who came to amputation were all diabetics with marked disease of the distal small vessels.

Degree of Obstruction

Poor results were more frequent in the patients with a higher degree of outflow obstruction (score zero to 4 and zero to 6). Approximately 80 percent of the patients in the two groups with the highest scores and the least degree of distal obstruction had good or excellent results as compared to only half of those in the lower-rated groups. There were, surprisingly, six patients with good or excellent results in the zero to three group; review of the x-rays showed that five of these patients had well developed collateral circulation via the geniculate arteries.*

Clinical Evaluation

Age, Diabetes and Hypertension

The age of the patient and the presence of diabetes mellitus or hypertension affected the results. Seventy-six percent of patients younger than 65 had good results compared to 55 percent of those 65 years of age and older ($P = < 0.05$). Nine patients were 75 or older; only three of them obtained a good result. Sixty percent of the diabetic patients were relieved of their symptoms, a significantly poorer result than the non-diabetic patients (78.5 percent good results) ($P = < 0.01$). Patients with hypertension did not do as well as the normotensives, only 64 percent of this group obtaining a good result ($P = < 0.05$). The outcome was not affected by the sex of the patient or whether the level of arterial obstruction was aortoiliac or femoropopliteal.

Sex, Diabetes and Level of Obstruction

The cases were divided into sets on the basis of sex, diabetes, and the level of obstruction, i.e., aortoiliac and femoropopliteal or a more distant level (Table 3). There were 28 patients with aortoiliac occlusion and 104 with femoropopliteal or more distal obstruction. Twelve

TABLE 3
Patients Undergoing Sympathectomy for Arteriosclerosis Obliterans

Tabulation by Diabetic Status, Sex, Level of Occlusion	
Non-diabetic Males with Aortoiliac Occlusion	13
Diabetic Males with Aortoiliac Occlusion	6
Non-diabetic Males with Femoropopliteal Occlusion	53
Diabetic Males with Femoropopliteal Occlusion	19
Non-diabetic Females with Aortoiliac Occlusion	4
Diabetic Females with Aortoiliac Occlusion	0
Non-diabetic Females with Femoropopliteal Occlusion	18
Diabetic Females with Femoropopliteal Occlusion	14

Tabulation by Diabetic Status, Sex and Level of Occlusion. The cases were divided into groups on the basis of the presence of diabetes, the sex of the patient, and the level of arterial occlusion. Those patients in whom the level of arterial occlusion was distal to the popliteal artery were included under femoropopliteal occlusion.

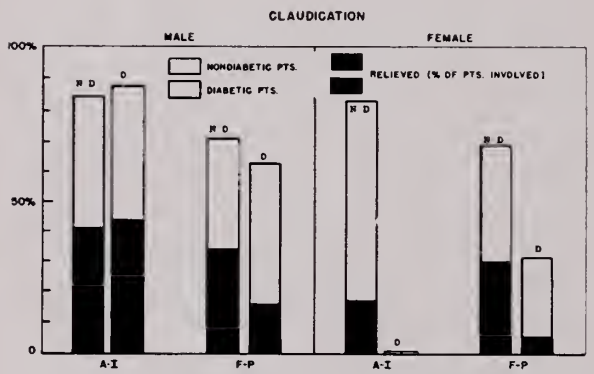
*See Test Your Word Score, page 523.

of the 28 patients with an obstruction of the aorta or iliac arteries had, in addition, an occlusion of the superficial femoral or popliteal artery.

Four major complaints were tabulated by the number of limbs involved.

Claudication

Intermittent claudication caused 99 patients distress and affected 120 legs. Claudication was less frequent in women. Following sympathectomy, amelioration was noted in almost half (47 percent) the limbs of the non-diabetic patients as compared to not quite one third (31 percent) of those who were diabetic ($P = < 0.10$) (Figure 2). Eventually the claudication was completely relieved in 16 and was diminished in 35 extremities. One year after sympathectomy 20 patients noted greater relief than they had noted three months after surgery, whereas only four patients were less relieved than they had been immediately following operation. Seven patients noted the return of claudication three or more years after sympathectomy.

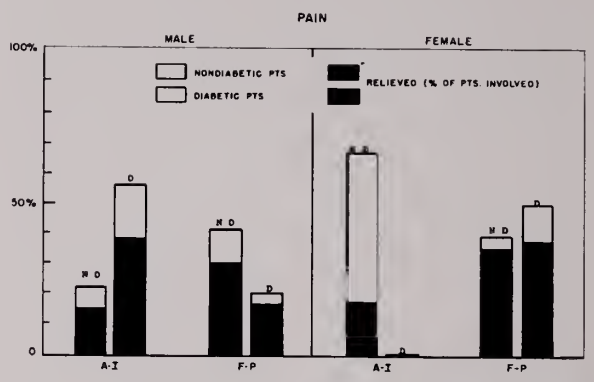


AI—Aortoiliac Occlusion FP—Femoropopliteal Occlusion
The outlined bar signifies the per cent of patients in each group who had claudication. The solid portion designates the proportion of pts with claudication who were relieved.

Fig. 2—Claudication. The outlined bar signifies the percent of patients in each group who had claudication. The solid portion designates the proportion of patients with claudication who were relieved of the symptom.

Rest Pain

Rest pain was the second most frequent complaint, affecting 67 legs in 58 patients. Following sympathectomy the pain disappeared in 75 percent of the limbs (70 percent of patients) whether the patients afflicted were diabetic or not (Figure 3). A somewhat greater proportion of patients with femoropopliteal occlusion obtained relief than did those with aortoiliac occlusion (78 percent vs. 60 percent) ($P = < 0.05$).

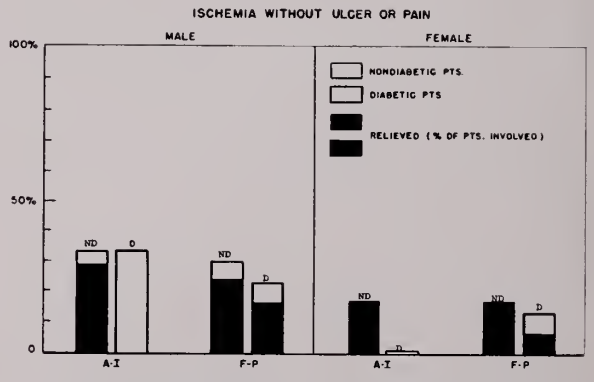


AI—Aortoiliac Occlusion FP—Femoropopliteal Occlusion
The outlined bar signifies the per cent of patients in each group who had pain. The solid portion designates the proportion of pts with pain who were relieved.

Fig. 3—Pain. The outlined bar signifies the percent of patients in each group who had pain in the leg or foot. The solid portion designates the patients with pain who were relieved.

Ischemia without Ulceration or Pain

It was noted on examination that cyanosis, coolness, numbness or cellulitis affected 55 legs which did not show tissue loss. A good result was obtained for 76 percent of the limbs, but the diabetic patients did not do as well ($P = < 0.10$) (Figure 4). Six legs required amputa-



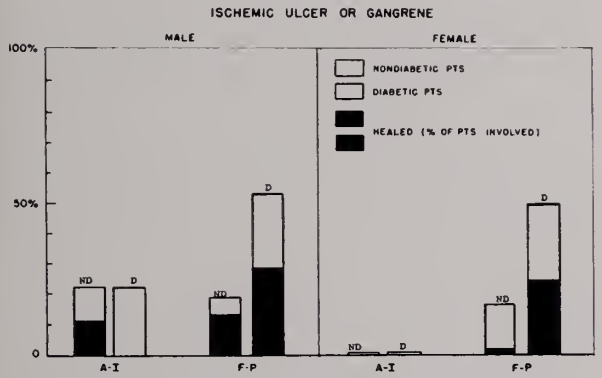
AI—Aortoiliac Occlusion FP—Femoropopliteal Occlusion
The outlined bar signifies the per cent of patients in each group who had ischemia. The solid portion designates the proportion of pts with ischemia who were relieved.

Fig. 4—Ischemia without Ulcer or Pain. The outlined bar signifies the percent of patients in each group who had ischemia. The solid portion designates the proportion of patients with ischemia who were relieved.

tion for progressive ischemia or cellulitis, three in diabetic and three in non-diabetic patients. Five of the patients who came to amputation were males with femoropopliteal occlusion.

Ischemic Ulcer or Gangrene

Loss of tissue is the most dreaded complication of arteriosclerosis because it is the one most likely to lead to amputation. An ulcer or an area of gangrene was found on the toes or feet of 49 extremities. The 25 patients with diabetes mellitus did not do as well as the entire group (65 percent good results for non-diabetic vs. 46 percent good results for diabetic patients) ($P = < 0.05$) (Figure 5). The ulcers did not heal prior to the death of two patients, and nineteen others required amputation. The two diabetic males with aortoiliac occlusion each lost a leg. Two additional patients came to amputation years later when new ulcers formed. In all, 53 percent of the ulcers, whether they involved the toes or the foot proper, healed.



AI—Aortoiliac Occlusion FP—Femoropopliteal Occlusion
The outlined bar signifies the per cent of patients in each group who had ulcer or gangrene. The solid portion designates the proportion of pts with ulcer or gangrene who were relieved.

Fig. 5—Ischemic Ulcer or Gangrene. The outlined bar signifies the percent of patients in each group who had an ulcer or gangrene of the foot or toes. The solid portion designates the patients in whom the ulcer or gangrenous area healed.

Follow-up Data

Follow-up information is available for 120 patients, all of whom had been operated a year or more prior to this study. The average follow-up is over five years; 48 patients have been traced for five or more years. For many patients the outcome, improvement or amputation, was obvious within several months.

Half of the patients are known to be dead. Necropsy examination was often not performed, as many of the patients died at home in small communities. The majority of the deaths were either sudden or followed a diagnosis of myocardial infarction. Deaths due to a pulmonary embolus were more common than would be expected (Table 4).

TABLE 4
Patients Undergoing Sympathectomy for Arteriosclerosis Obliterans

Follow-up Data			
Range—1 to 16 yrs		Average—5.5 yrs	Median—4.4 yrs
Dead	—49%	Alive	—51%
Average Survival	—5.6 y	Average Survival	—5.4 y
Median Survival	—3.7 y	Median Survival	—5.0 y
Known Causes of Death			
Pulmonary Embolus	— 6 pts	Myocardial Infarction	—20 pts
"Sudden Death"	—15 pts	Cerebrovascular	
Cancer	— 6 pts	Accident	— 6 pts

Follow-up Data. Follow-up data were obtained either by specific inquiry or by re-examination at the clinic or hospital. The information was available for 120 patients operated a year or more prior to this study. Known causes of death are listed.

Of the 66 surviving patients, half have lived more than five years since sympathectomy.

Discussion

Hypertension and Diabetes

As in other series of patients undergoing sympathectomy for arteriosclerosis obliterans there was in this one a high incidence of hypertension and diabetes. With the exception of Szilagy,[6] most authors have reported poorer results in diabetic patients after sympathectomy. This difference was statistically significant in our own study, which also showed significantly poorer results for patients with hypertension.[1,5,6]

Tobacco

Abramson et al.[14] reported that non-smokers had fewer episodes of trophic* changes and more often experienced spontaneous improvement in their claudication than did those who smoked. We warn our patients that smoking has a deleterious effect on the peripheral arteries.

*See Test Your Word Score, page 523.

Collateral Circulation

One suspects that some of the improvement, perhaps 50 percent, observed following sympathectomy may be due to the spontaneous development of collateral circulation.[2] This factor has made the evaluation of results of sympathectomy difficult. Digital plethysmography has shown that muscle perfusion is only transiently increased by sympathectomy, and objective improvement in the patient's response to exercise could only occasionally be demonstrated.[2,3,4] Both Abramson[14] and Shaw[11] found the incidence of improvement in claudication to be the same in the operated and the non-operated patients. Although patients undergoing sympathectomy seldom develop increased claudication during the first three years after operation, after five to 10 years one third of the patients in each group noted more severe claudication.

On the other hand, Van de Berg et al.[15] demonstrated experimentally that in the presence of critical arterial stenosis muscle function improved following sympathectomy. They attributed this to an increase in distal arterial pressure. Many clinical studies indicate that lumbar sympathectomy does at times favorably influence the course of intermittent claudication. King et al.[6] found that 18 percent of their sympathectomized patients could walk an unlimited distance and an additional 24 percent noted an increased walking distance before the onset of pain. Other authors have noted improvement in walking distances after surgery in 15 to 30 percent of patients,[1,5,16,17,18] and Heringman[5] found that two thirds of his patients had improved oscillometric readings after sympathectomy.

Our own work indicates that claudication is relieved within a short time in 15 percent of patients undergoing sympathectomy. Subsequently, another 20 percent note relief during the ensuing first postoperative year due to spontaneous improvement in the circulation.

Ischemic Tissue

Haimovici[1] and Szilagy[7] found that about 70 percent of their patients with rest pain or ischemic tissue changes without gangrene or ulceration were improved after operation, a figure somewhat better than that reported by King et al.[6] and quite close to that noted in the present study. The modest gain in the late healing of ischemic ulcers and a small reduction in the number of amputations after sympathectomy can be attributed to the improvement in skin blood flow which occurs when the subject is standing or is exposed to a cool environment.[2,4] The rate of healing reported by Abramson,[14] Haimovici,[1] and Heringman[5] was almost identical to that in the present study.

Post-sympathectomy neuralgia most likely occurs only in patients who have had normal sympathetic enervation prior to surgery. This may explain the similarity of results obtained in patients who had neuralgia and those who had a positive nerve block or sweating test. Its occurrence, which is probably more common than reported in the literature or in this study, appears to have retrospective value in predicting the final outcome.

Szilagy[7] could not correlate the angiographic pattern on arteriography with the results obtained following sympathectomy. We could discern no difference in overall results, either, between patients with aortoiliac and those with femoropopliteal occlusion; but when the distal outflow was studied rather than the more proximal angiographic pattern, there was good correlation between the degree of outflow obstruction and the final result.

Skin Temperature

As a better method of selecting patients for sympathectomy Haimovici[1] stressed the prognostic value of measuring the rise in skin temperature following a nerve block; Myers and Irvine[2] demonstrated that the more prompt and the greater the degree of reactive hyperemia the better were the results. It is our practice currently to select patients for sympathectomy on the basis of their age and general condition, the degree of peripheral ischemia and necrosis present, and the absence of a situation amenable to arterial reconstruction. Advanced age or gangrene or large deeply penetrating ulcers of the foot, especially in diabetics, are contraindications to surgery. Candidates for surgery must show perspiration over the legs and feet or a rise in skin temperature following a

nerve block. Many elderly patients and many with diabetes mellitus will have negative results on testing, due to loss of sympathetic nerve function. Arteriography may show too extensive obliteration of the distal vessels to warrant sympathectomy. We do not consider the operation to be indicated for the prophylactic treatment of ischemia or for the treatment of claudication as the sole symptom.

Meticulous local care, discontinuing smoking and awaiting development of collateral circulation will help many patients with ischemic tissue changes. With careful selection sympathectomy will effectively increase the superficial circulation and contribute to the relief of symptoms in at least 20 percent more patients than would otherwise obtain spontaneous benefit.

The significantly better results accomplished when patients were selected for operation by testing for the presence of sympathetic nerve function can be cited as evidence for the value of sympathectomy. The operation has proved to be safe and simple, and to offer modest benefits to patients, especially the younger nondiabetic patients, with peripheral arteriosclerosis obliterans.

Summary and Conclusions

One hundred eighty-one lumbar sympathectomies were performed for the treatment of ischemic symptoms, rest pain or tissue loss due to arteriosclerosis obliterans. Diabetes mellitus was present in 31 percent of the patients and hypertension in 40 percent. At least 80 percent of the patients used cigarettes. There were no operative deaths, and morbidity was mainly limited to post-sympathectomy neuralgia.

Although 70 percent of the affected limbs were improved after sympathectomy the results were significantly better for patients who demonstrated perspiration over the legs, a rise in skin temperature following nerve block, or post-sympathectomy neuralgia. The elderly, diabetic, and hypertensive patients did not as often obtain a good result following sympathectomy, and the differences were significantly valid.

Though the outcome was not affected whether the occlusion was aortoiliac or femoropopliteal, the results could be related to the degree of distal outflow obstruction. A very high degree of outflow obstruction should be considered a relative contraindication to sympathectomy.

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14-18. May be secured from the author or the reprints.

Derivatively Speaking

Allyl—a univalent radical—from Latin *allium* (garlic) and Greek *hyle* (matter).

Religion and the Law

Organ Transplants*

ANOTHER QUITE new kind of ethical problem has arisen because of the present possibility, due to scientific advances, of transplanting certain vital organs, especially the heart and the kidney. Particularly in the case of the heart it is presently impractical to employ for transplantation a heart that has ceased to beat. Consequently, to have any hope of success, the organ must be taken from another individual who is not dead in the conventional sense, i.e., one whose heart is still beating. Here both scientific and ethical, as well as legal considerations are involved.

When is an individual dead? This is not a simple question to answer. The conventional answer is that when breathing and heart action stop, a person is dead. But scientific and technical advances now allow one to keep the brain, muscles, digestive system and metabolic processes going for a long time after the heart stops and natural breathing has ceased or been stopped. Furthermore, if artificial respiration is applied, the heart can be made to continue to beat for hours or days after spontaneous breathing ceases. The brain may show no evidence of any activity and the heart would stop promptly if the assist mechanisms were withdrawn. The important point is that all living cells in the body do not die, i.e., cease to function, simultaneously.

Then when is an individual dead? The law has accepted the rule that the time of death is ordinarily set at the time an attending physician declares that his patient has expired. No specific criteria are demanded.

The lack of any specific criteria as to the legal definition of death poses an ethical problem for medical investigators who are trying to make transplantation of vital organs become a workable procedure. They need live organs. To put it very bluntly they need hearts from human subjects before these subjects are dead, in the sense that the man on the street defines death.

The question thus becomes one of whether it is ethically proper for a physician, or a group of physicians, to say: "This person is in essence dead," when it is practically certain that no known therapeutic procedure could revive him. "Practically certain" really means only that in dealing with perhaps a thousand patients who showed a flat electroencephalogram for a given period of time, not one survived discontinuance of life-assist mechanisms. This means only that the statistical chance of anyone in that state being able to survive is less than one in a thousand. Is this certainty? Of course not. It is, however, high statistical probability. It is easy, perhaps, for the detached observer to say that a probability of 0.001 of being wrong approaches zero, but it is not zero. Even if the number becomes <0.000001, it is not zero.

I am stressing the point that probability numbers are entering into ethical judgments. I do not say that they should not; I only point out the fact that they do. The question obviously arises as to whether a physician is justified in calling his patient dead when in fact there are vital signs still showing—e.g., the heart beat, and he has only a high statistical probability in his favor when he says the brain is not capable of regaining some degree of normal function.

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*See April issue, page 368, for previous article.

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Oral Manifestations of Uremia

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THE SYNDROME of uremia is reflected in many organ systems. In the oral cavity, alterations may include xerostomia,¶ spontaneous gingival bleeding, or severe stomatitis.

Barié's[1] classic description of uremic stomatitis presented in 1889 remains one of the most complete on this subject. Two forms of stomatitis were described. The more common erythemopultaceous type was characterized by a dry, burning, oral cavity covered with a thick, gray exudate. Removal of this membrane revealed a red, dry (nonulcerative) mucosa. The rare ulcerative form had the same clinical features as did the erythemopultaceous variety but had underlying mucosal ulcerations. In Barié's cases, the ulcerations were all less than 1 cm in diameter. After the initial description, a number of such cases were reported.[2-10]

The cause of uremic stomatitis continues to remain unknown; however, the lesion appears to be related to the biochemical abnormalities associated with the underlying renal insufficiency. This is dramatically apparent when, with little or no specific oral treatment, the stomatitis will often completely disappear within 48 hours after dialysis is begun. Hempstead and Hench[2] have discussed the several hypotheses pertaining to the etiology of the stomatitis.

Bliss[4] believed that the ulcers were due to local mucosal irritation from ammonia, which was liberated from salivary urea in the oral cavity by the action of urease contained in teeth calculus. He noticed that the ulcers diminished when the calculus was removed even though levels of blood urea nitrogen remained unchanged. To support his theory, he sealed three glass tubes against the oral tissues of a dog, the control tube containing saline, and the other two ammonium hydroxide and ammonium sulfate, respectively. Ulcers occurred beneath the two tubes containing ammonia, being more severe under the tube of ammo-

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¶See Test Your Word Score, page 523.

nium hydroxide. Black[6] also considered this condition a chemical stomatitis caused by the caustic effect of ammonium carbonate.

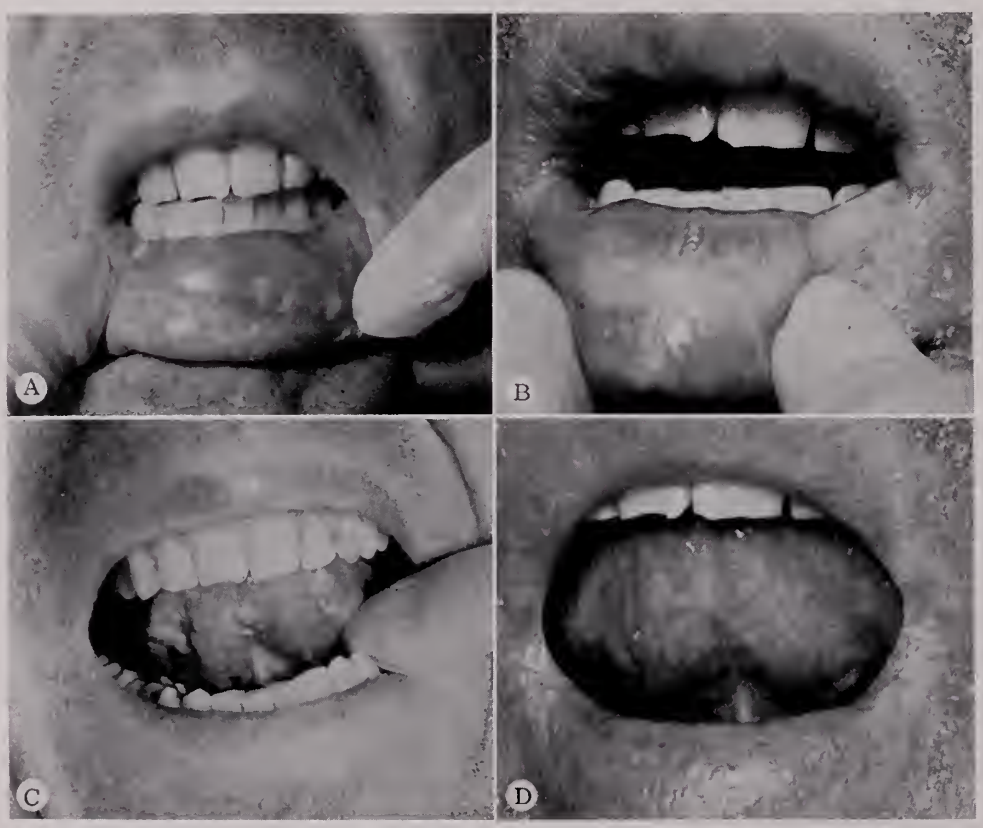
In his thesis, "A Salivary Index to Renal Function," Hench[11] demonstrated that concentration of salivary urea was approximately 80% of blood urea concentration. Hench and Aldrich[12] believed that ammonia was formed from this urea primarily by bacterial hydrolysis; however, they did not study the relationship of specific bacteria to stomatitis. Black[6] did not find any specific bacteria in the scrapings from the oral lesions, and Bereston and Keil[5] could culture *Bacillus proteus (P. vulgaris)* and *Bacillus diphtheriae (Corynebacterium diphtheriae)* from only one patient.

Beaney[9] believed that the accumulation of superficial squamae and the alteration of the bacterial flora by the changes in pH predisposed the patient to infection with *Candida albicans*; however, *Candida* spores were recovered in the blood culture from only one patient.

In addition to the stomatitis, several other oral complications of uremia have been noted. Xerostomia has been a frequent complication.[1,3,13-17] Hess[15] noted that sialorrhea* was present during the early stages of uremia; the saliva was thin and contained decreased amounts of ptyalin. He believed that sialorrhea later developed into xerostomia because of the lack of ptyalin. Chargin and Keil[3] considered that xerostomia was a result of the compensatory polyuria, with dehydration of all tissues.

Gingival bleeding also may be seen. Wright[18] reported five uremic patients who had gingival bleeding but no associated oral lesions. Gelfand[19] presented six patients who had gingival bleeding, two of whom also had vaginal bleeding. Several other investigators reported this complication.[13,20-22] Castaldi, Rozenberg, and Stewart[22] studied 19 uremic patients, seven of whom had abnormal bleeding, and concluded that the bleeding was due to a reversible qualitative defect of the platelets, perhaps an abnormality of the platelet surface or failure to release platelet factor III. They noticed that the

*See Test Your Word Score, page 523.



Figure—A 34-year-old white man with typical lesions on the vermilion border of the lower lip (*A* and *B*) and ventral surface of the tongue (*C* and *D*) before (*A* and *C*) and immediately after (*B* and *D*) hemodialysis.

bleeding was corrected by dialysis and therefore considered this to be the biochemical effect of renal failure. Schreiner and Maher[20] also were of the opinion that the bleeding was due to a qualitative defect of the platelets.

Because of the discrepancies in the literature regarding the incidence of uremic stomatitis and the associated oral findings and the impression that the incidence is greater than previously reported, a retrospective study was undertaken.

Methods and Materials

The histories of 70 consecutive uremic patients who had undergone peritoneal dialysis or hemodialysis during a two-and-one-half-year period ending August 1967 were reviewed. The patients were divided into three groups. Group 1 consisted of patients who had a definite diagnosis of uremic stomatitis during observation and treatment at our clinic. Group 2 was composed of patients who had questionable evidence of uremic stomatitis. This group included patients with herpes simplex, nonspecific oral ulceration, oral desquamation, or a history of stomatitis prior to admission at our clinic. Group 3 consisted of patients who were without evidence of stomatitis. The records of these patients were reviewed, and specific references to xerostomia, gingival bleeding, oral petechiae, ecchymosis, and stomatitis were noted.

Findings

Of the 70 patients, 20 had xerostomia of a sufficient degree to be mentioned by the examining physician, six had oral petechiae or ecchymosis, and three had gingival bleeding not associated with periodontal disease. Twenty-eight patients in the series died of their renal disease (Table).

More than 50% of patients who died from renal disease had oral findings. Nine had uremic stomatitis: six definite and three questionable. Of the patients who died, nine had xerostomia and one had oral petechiae.

Uremic stomatitis in 10 patients (14.3%) was seen during their period of observation at our clinic (Figure). Both the ulcerative and nonulcerative forms (as described by Barié[1]) were found, often in the same patient. Six of the 10 patients died 12 days to 10 months after the onset of the stomatitis. The stomatitis seemed to be related to the peak level of the blood urea. No patient had more than a single episode of stomatitis. All but one patient had a blood urea level of more than 300 mg/100 ml at the onset of stomatitis, and in most patients, the level was greater than 400 mg. The stomatitis lasted from one to 11 days and tended to disappear with dialysis and the subsequent lowering of the blood urea level. Of the 10 patients with stomatitis, four had xerostomia, and three of the four died. Two of the 10 patients were completely edentulous. Petechiae or ecchymosis was present in both of these patients, one of whom died in acute renal failure. One of the 10 patients with stomatitis had spontaneous gingival bleeding; another had xerostomia and petechiae.

There was questionable evidence of uremic stomatitis in five patients; three died from renal disease. Of the five patients in this group, two had xerostomia.

Fifty-five patients had no evidence of uremic stomatitis; however, many of these had oral complaints. Fourteen patients in this group had xerostomia; five died of renal disease. Four patients had oral petechiae or ecchymosis, and two had spontaneous gingival bleeding; none of these six patients died.

Comment

Uremic stomatitis must be considered an ominous sign. Although 28 (40%) of the 70 patients in our series died of renal disease, six

TABLE

Relationship of Uremic Stomatitis to Other Oral Manifestations in 70 Consecutive Uremic Patients Who Had Undergone Peritoneal Dialysis or Hemodialysis

		Oral findings		
Group	No. of patients	Zero-stomia	Petechiae or ecchy-mosis	Gingival bleeding
Uremic stomatitis	10(6*)	4(3)	2(1)	1(0)
Questionable uremic stomatitis	5(3)	2(1)	0(0)	0(0)
No uremic stomatitis	55(19)	14(5)	4(0)	2(0)
Total	70(28)	20(9)	6(1)	3(0)

*Number of deaths in parentheses.

of the 10 (60%) with uremic stomatitis died within 10 months of its onset. The remaining four patients have either received a renal allograft or are on chronic hemodialysis. As demonstrated by Bliss,[4] the stomatitis is probably a chemical burn, probably due to the ammonia liberated by the action of urease on the salivary urea. As evidenced by the presence of uremic stomatitis in completely edentulous patients, the urease cannot be solely from the calculus on the teeth. Several species of bacteria, some of which are included in the normal oral flora, produce urease.[23] The variations of the normal flora among different persons may explain the sporadic occurrence of the stomatitis. At least two conditions must be present (and perhaps other as yet unknown factors) for the development of uremic stomatitis, namely a high content of salivary urea and either abundant calculus or, perhaps more important, bacteria with the ability to decompose urea.

The hypothesis of a pure bacterial or mycotic infection is unacceptable because it does not explain the appearance of the oral lesion coinciding with the peak of azotemia or the significant response of the stomatitis to dialysis.

Xerostomia was the most common oral finding in the uremic patient. Direct involvement of the salivary glands[24] and retrograde sialadenitis[22] have been implicated as possible etiologic factors for the xerostomia. We were unable to document a single case of parotid or submandibular salivary gland pathology in our series. Holmes and associates[25] found that in renal failure the salivary flow was significantly reduced at the time when fluid restriction was most pronounced and tended to approach normal when the patients were adequately hydrated. Dehydration as the predominant cause of xerostomia seems unlikely since many of these patients are fluid-overloaded. Most likely the xerostomia results from a combination of factors leading to mouth-breathing.

As has been noted, spontaneous gingival bleeding is not an infrequent finding. Many of the patients with such bleeding also have epistaxis which, with the subsequent crusting and nasal obstruction, encourages mouth-breathing. In addition, some patients at the time of their admission were taking reserpine. It has been our experience that the side effects of reserpine in the presence of renal failure are increased; nasal stuffiness is one such side effect and similarly encourages mouth-breathing. Furthermore, these patients tend to hyperventilate as a result of their metabolic acidosis. As would be expected, the presence of a mechanical xerostomia did not seem to contribute to the general physical state of the patient and was not associated with an increased mortality rate.

As Castaldi and associates[22] have proposed, the petechiae, ecchymosis, and gingival bleeding observed in patients with renal failure are probably secondary to a thrombopathy.

Several oral conditions may be confused with uremic stomatitis: leukoplakia, lichen planus, *C. albicans* infection, herpes simplex, and erythema multiforme. Aspirin burn, white spongy nevus, and gingivitis at times can mimic uremic stomatitis. These conditions should be seriously considered in the patient who does not present with uremia. A carefully taken history and carefully conducted clinical examination should lead to the proper diagnosis.

Treatment for stomatitis is palliative. The overlying plaque of the lesions is cleansed with half-strength hydrogen peroxide; the ulcerative lesions are cauterized with negatol (Negatan), and triamcinolone (Kenalog) in a protective paste (Orabase emollient) is applied topically on each. This treatment is carried out three to four times each day. The direct application of 5% lidocaine viscous prior to meals is also of benefit; this regimen tends to give good symptomatic relief but does little to heal the lesions. Correction or stabilization of the biochemical abnormalities associated with the underlying renal dysfunction tends to bring immediate and complete alleviation of the oral symptoms. Although local treatment is palliative, it should not be neglected, because if oral intake is painful, the patient is less likely to adhere to the prescribed diet, thus making alleviation of the uremic symptoms more difficult.

Summary

A study of 70 uremic patients who had undergone dialysis revealed that 10 had uremic

stomatitis and that six of the 10 died of renal disease within 10 months of the onset of the stomatitis. The stomatitis probably is a chemical burn caused by the action of bacterial urease on the salivary urea, with the subsequent liberation of ammonia. The appearance of stomatitis in the uremic patient is an ominous sign. Of the 70 patients in the series, 29 had xerostomia or an oral bleeding problem; but no prognostic significance could be placed on either of these findings. The definitive treatment depends on the correction of the biochemical abnormalities.

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Walking Off Your Troubles

Sometimes I think that the tensions which plague modern Americans stem less from troubled times than from the automobile. With little occasion for walking, we store up psychomotor energies our grandparents would have left along the sidewalks or the bridle paths. Certainly, rhythmic body movements help to fight off tenseness and emotional upset, even to the point of building courage for heroic feats, as the almost universal rites of the war dance have proved. When you want tranquility, plain walking, rowing or other repetitive simple movements often fill the bill.*

*John E. Eichenlaub, M.D.: The Minnesota Doctor's Home Treasury of Unusual Stress Easers, 1964.

A Trio of Female Centenarians

Attaining the venerable age of five score and a bit more has not been the prerogative of the male sex alone; some women also have achieved triumphant centenarian status by flouting the Biblical three-score-and-ten allotment. Three such come to mind: two English-born and one Irish-born.

Lady Smith (1773-1877), nee Pleasance Reeve and wife of Sir James Edward Smith, was a true English gentlewoman, stately in demeanor yet lively in spirit, whose pursuits were so varied as to include on the one hand an active interest and participatory involvement in public events, political issues, and ecclesiastical matters; and on the other hand a profoundly personal commitment to the study and appreciation of nature, poetry, history, and hymnody.

"At the age of one hundred Lady Smith was a marvel. . . . She was, in fact, so extremely well-preserved as to set at naught ordinary standards of comparison. She hardly betokened age. Her countenance and figure were still impressive. The mobile features had nothing of the pallor associated with extreme old age. Her eyes still sparkled, and nearly all her teeth were intact. She hardly knew what illness was. Her sight, however, was beginning to fail, though she still continued to write letters in a clear and beautiful caligraphy such as one seldom sees in this typewriting age. . . . Her hearing, on the contrary, remained excellent, and she was keen to converse on public events of the day.

"Lady Smith was a striking illustration of the truth of the remark that the most valuable qualification for a happy and tranquil old age is the capacity for enjoying thoroughly the specific phases of one's own natural activity."

Also to the manner born was Mary Elizabeth Haldane (1815-1925), nee Mary Elizabeth Burdon and wife of Robert Haldane. She was a paragon in that she perpetuated an illness-and-accident-prone body to the century mark. A truly matriarchal type blending majesty, authority, and benignity, she enjoyed the unique honor of being sought out and deferred to by young and old, both public and private figures, who recognized and valued her judgment, discretion, insight, and wisdom—always deeply charged with an emphasis on spiritual values.

Invalided within the house during her latter years "Mrs. Haldane read extensively in various languages, not 'light literature,' but memoirs, histories, even philosophical works. She also beguiled the time by conducting a voluminous correspondence with all sorts of people, and by diligent perusal of the newspapers whereby she kept abreast of the momentous happenings of her last years. Her days as an invalid were also agreeably interrupted by visits from those who held the foremost places in public life:" archbishops, soldiers, statesmen, and men of letters.

"And when the day's interviews were over, the venerable lady would feast her eyes on the noble contour of the Grampians* or watch the beautiful sunsets, or listen with delight to the sonatas of Beethoven and Mozart being played on a small piano in her bedroom. She also spent some time in reading. Those who heard her said she was very impressive when she gave forth in deep, sonorous tones her favorite passages in the Bible."

Splendid health all her life, except for an attack of bronchitis at age 102, the Honorable Katherine Plunket (1820-), member of the distinguished Irish House of Plunkett, celebrated her 110th birthday on November 22, 1930—with congratulations from King George and Queen Mary, and perhaps with a sump-

(Continued on Page 530)

*See Test Your Word Score, page 523.

Fetal Acid-Base Studies in Labor*

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EVER SINCE JAMES[9] in 1958 showed that there was a significant relationship between the condition of the newborn and its acid-base balance, there has been increasing interest in methods of measuring fetal acid-base status. In 1962, Saling[17] devised a method of sampling fetal scalp blood and clearly established its clinical usefulness in evaluating the condition of the fetus. Subsequently a number of centers have instituted fetal scalp blood sampling.[2,6,8,10,21] The purpose of this paper is to present some basic aspects of acid-base balance in the fetus in order to more clearly define its usefulness in various clinical situations.

Fetal Acid-Base Physiology

Although fetal scalp blood may be modified by local pressure and edema, the acid-base parameters of arterialized capillary blood are in fact intermediate between that of the umbilical artery and the umbilical vein.[4,5,6,10] Table 1 shows the components of the actual pH of the fetus. The respiratory component is dependent on the carbon dioxide (CO_2) content of the blood, a component always higher in the fetus than in the mother.[12,19] Equilibrium is easily maintained provided the utero-placental-umbilical circulation is intact. The metabolic components are bicarbonate, plasma protein and hemoglobin. Although at a somewhat slower rate than that of CO_2, there is also placental transfer of metabolic components.[3,13,16,17,20] As CO_2

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TABLE 1
Actual pH of the Fetus

A. Respiratory Component
1. Carbon Dioxide Content
B. Metabolic Components
1. Bicarbonate
2. Buffer Base
3. Hemoglobin

and nonvolatile acids cross the placenta, fetal acidosis may therefore be due to a number of factors as shown in Table 2.

TABLE 2
Fetal Acidosis

- A. Maternal Acidosis
  - 1. Respiratory
    - a. Breath-holding
    - b. Respiratory Obstruction
  - 2. Metabolic
    - a. Prolonged Labor
    - b. Dehydration
    - c. Diabetes
- B. Fetal Hypoxia
  - 1. Uteroplacental Insufficiency
  - 2. Umbilical Cord Compression
  - 3. Placental Separation

An excellent review of the acid-base balance of the fetus has been presented by Beard.[1] Due to the Bohr effect, the lower the pH, the lower the oxygen saturation at a given oxygen tension (pO_2). In the intervillous space fetal acidosis results in a decreased transfer of oxygen to the fetal red blood cells. On the other hand, in the fetus the Bohr effect results in an increased availability of oxygen to the tissues. However, severe acidosis produces widespread biochemical changes and eventual tissue damage.

Methodology

Fetal Blood Sampling

Fetal scalp blood is easily obtained.[11] Contraindications to sampling are chorioamnionitis, which may result in infection in the fetus, and face presentation. The membranes must be ruptured and the cervix dilated at least two or three cm. An endoscope, the type commonly used in amnioscopy, is closely applied to the fetal scalp to prevent contamination with blood and amniotic fluid. The scalp is sprayed with a refrigerant which results in reflex vasodilation. A silicone solution is applied to aid in the formation of a large drop of blood without contamination by fluid about the scalp. The scalp is incised with a scalpel whose blade extends only two mm. beyond a guard and is two mm. in width. It is important to maintain strict asepsis.

Measurement of Acid-Base Parameters

Approximately 0.1 ml. of blood is drawn into a sterile heparinized glass capillary tube. A small wire is put into the tube, the ends are sealed, and mixing of blood is accomplished with a magnet. The actual pH is measured immediately in an Astrup apparatus which is kept warm in the labor suite at all times. Two other samples of fetal blood are placed in tonometers through which CO_2 is flowing, one of low and the other of high concentration. After adequate equilibration the pH is measured in each of the tonometers and the values are plotted on a Siggaard Andersen nomogram.[18] Similar determinations are carried out on maternal blood. Maternal studies have been made on arterial blood,[8] venous blood obtained without stasis,[3] and arterialized capillary blood.[12] There would seem to be no preference, as the intervillous space contains a mixture of arterial and venous blood.

A Siggaard Andersen nomogram is presented in Figure 1. Points A and B were plotted after measuring the pH of blood which had been equilibrated with high CO_2 and low CO_2 concentrations and a line was drawn through the points. The actual pH of the sample, 7.38, was plotted on this line (C). The CO_2 tension (pCO_2), buffer base, standard bicarbonate and base excess (deficit) values are obtained: pCO_2 is 23 mm Hg., base excess is –12, standard bicarbonate is 14 and buffer base is 33. Buffer base, standard bicarbonate and base excess constitute the metabolic components. An equilibrated or metabolic pH can be read off the nomogram with a line dropped from where the line crosses 40 mm Hg. to the pH scale. This point represents the pH with a pCO_2 of 40 or the "pH qu 40" of Saling.[17] This value, or the base excess, is commonly used in expressing the metabolic status. As can be seen from this nomogram, because of the relatively low pCO_2,

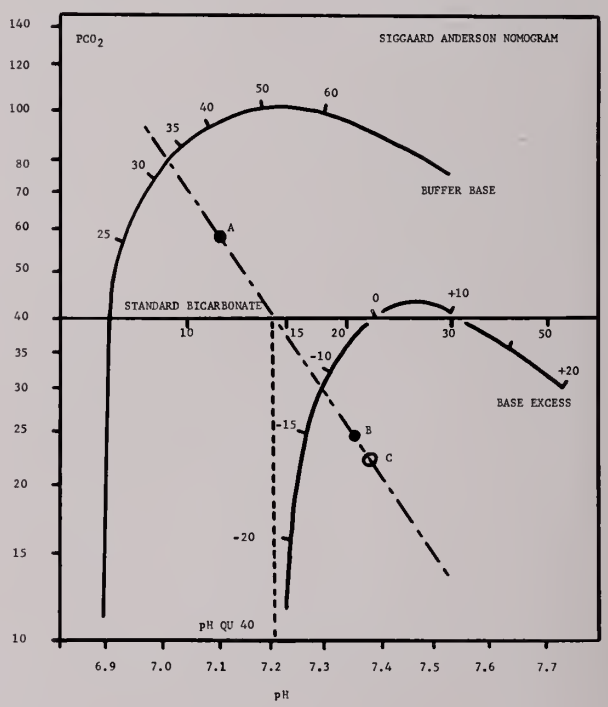


Fig. 1—Siggaard Andersen nomogram. Points "A" and "B" have been plotted after obtaining pH measurements on blood samples equilibrated with known high and low CO_2 concentrations and a line drawn through these points. The actual pH of the blood sample (C) has been placed on this line where it corresponds to the pH scale. Values for metabolic components are read off on the corresponding curves and the equilibrated pH determined by dropping a line to the pH scale from where the line crosses pCO_2 of 40 mm Hg.

the actual pH is considerably higher than the equilibrated pH. Thus, metabolically the fetus is more acidotic than one would be led to believe if only the actual pH were obtained. Table 3 shows the different metabolic parameters which are utilized in evaluating the fetus. The actual pH of the fetus does not necessarily reflect its true acid-base balance.

TABLE 3
Acid-Base Parameters

Parameter	Equilibrated Parameter*	Normal Range
Buffer Base (BB)	Base Excess (BE) or Base Deficit (BD)	+5 to −5
Bicarbonate (HCO_3)	Standard Bicarbonate	18 to 25
pH	pH qu 40 (SALING)	over 7.20

*Equilibration at pCO_2 40 mm Hg.

Interpretation of Acid-Base Values

A number of points need to be emphasized. It has been shown that there is a rapid transfer of CO_2 across the placenta.[12] Hyperventilation markedly lowers the CO_2 content and pCO_2 of the blood with elevation of the pH. This change is reflected in minutes with a lower pCO_2 and a higher pH in the fetus. On the other hand, Newman et al. demonstrated that when breathing an increased concentration of CO_2, the pCO_2 of the mother rapidly rises and the fetus shows a similar change.[12] The pH decreases in both circulations.

There is also transfer of nonvolatile acids across the placenta.[7,13,16,20] The base deficit of the fetus parallels that of the mother but is usually greater. Ammonium chloride administration to the mother results in acid-base changes in the fetus.[7,13] Likewise, sodium bicarbonate increases standard bicarbonate and pH with similar changes in the fetus.[13] Mild passive metabolic acidosis of the fetus, as a result of maternal metabolic acidosis, is usually of little significance.[7] However, as in diabetes mellitus, severe metabolic acidosis may be disastrous for the fetus.

It must be emphasized that isolated observations provide no information concerning the duration of an abnormality or later changes.

In summary, for meaningful evaluation of the fetal acid-base status, it is necessary to (1) evaluate all components, (2) simultaneously evaluate the maternal status, (3) perform serial studies.

Case Histories

The fetus is in jeopardy when metabolic acidosis of a significantly more severe degree than that of the mother is present, particularly when serial studies show the difference to be increasing. Severe metabolic acidosis is always accompanied by respiratory acidosis. Four case studies will illustrate a number of these points.

Case 1

The actual pH and equilibrated pH of patient A.H. and her fetus are presented in Figure 2. This nulliparous patient had acid-base studies of her blood and fetal scalp blood after one hour of the second stage of labor. All values were within normal limits. At the time of the second evaluation, one hour later, the actual pH of the mother and fetus had dropped and were, in fact, at borderline levels. However, both were in normal metabolic status.

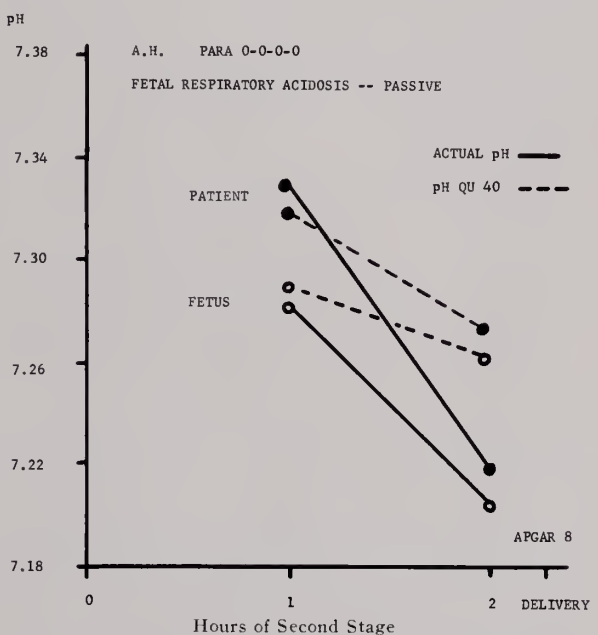


Fig. 2—Initially normal actual pH and equilibrated pH values were obtained in the mother and the fetus. One hour later there was a marked drop in the actual pH of both. However, only minimal metabolic acidosis was present, indicating that changes in actual pH were due to CO_2 retention.

The lowering of the actual pH was due to breath-holding in the last stages of labor with CO_2 retention. The infant was delivered approximately 20 minutes later with an Apgar of 8 at one minute. This case illustrates how a low actual pH may erroneously indicate that the fetus is in trouble.

Case 2

Similar studies are shown in Figure 3 on patient R.A. The actual pH and the equilibrated pH were obtained after one hour of second stage. Repeat studies were

performed two hours later and both showed a moderate fall in actual pH. The equilibrated pH of the mother dropped to acidotic levels, while the equilibrated pH of the fetus also dropped but was higher than the maternal.

Thus, as labor progressed with strenuous muscular activity, there was development of maternal metabolic acidosis which was transferred to the fetus. Delivery occurred 30 minutes later and the infant had an Apgar of 9 at one minute. The infant had passively acquired mild metabolic acidosis which was not significant.

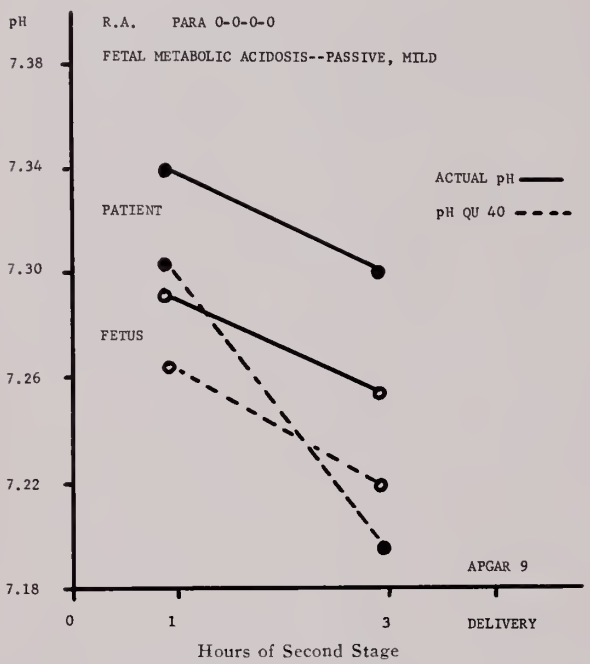


Fig. 3—Two hours after obtaining normal actual pH and equilibrated pH values in the mother and the fetus there was minimal lowering of the actual pH. Nevertheless, there was a marked fall in the equilibrated pH values, this fall more marked in the mother. Compensatory respiratory alkalosis prevented a more marked fall in the actual pH and obscured the metabolic acidosis.

Case 3

A nulliparous female in the second stage of labor was also studied on two occasions; the results are shown in Figure 4. The actual pH and equilibrated pH of the patient and her fetus were initially within normal limits. One-half hour later there was a moderate decrease of the actual pH of the mother and fetus as well as the maternal equilibrated pH. However, there was marked lowering of the fetal equilibrated pH, from 7.255 to 7.190.

As can be seen, there was divergence of the fetal and maternal equilibrated pH values. The infant was delivered approximately 20 minutes later with an Apgar of 5 at one minute. This case points out that when there is fetal metabolic acidosis more severe than that of the mother the fetus is likely to be in jeopardy.

Case 4

A 40-year-old nulliparous patient had induction of labor at 42½ weeks. Artificial rupture of membranes was followed by a short latent phase of labor. The acceleration phase was normal but there was a marked prolongation of the deceleration phase with mild fetal tachycardia. Fetal blood studies were performed on eight occasions during the latter part of the acceleration and deceleration phases. After three and one-half hours without progress cesarean section was performed. It was felt that oxytocin stimulation of labor was contraindicated in this elderly primigravida in spite of a normal bony pelvis and a normal acid-base balance of the fetus. An infant with an Apgar of 8 at one minute was delivered.

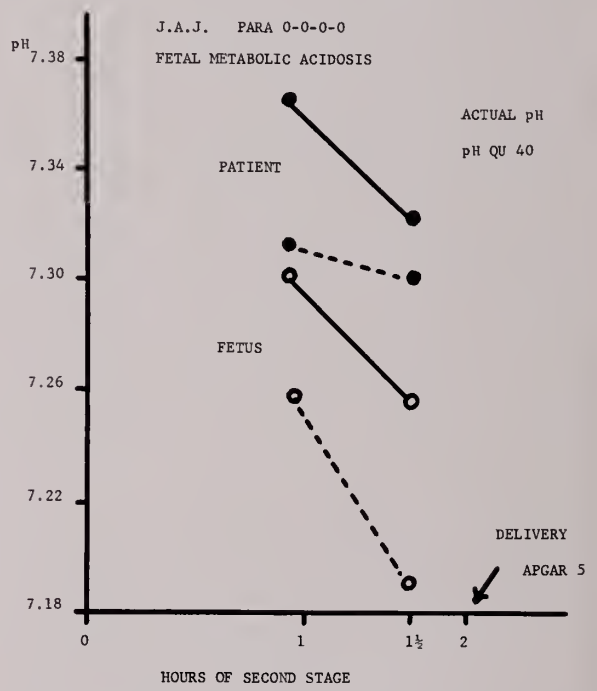


Fig. 4—Initially the actual pH and metabolic pH values of the mother and the fetus were in the normal range. Although the actual pH values were only slightly lower than one-half hour later, the fetal equilibrated pH was much lower than the mother's and below the normal range. The infant's Apgar rating was 5. The actual pH was misleading.

Figure 5 shows the actual pH, the equilibrated pH and the base excess of the fetus over four hours of the first stage of labor. It can be seen that there was wide variation of the pH, due to fluctuating CO_2 content of the maternal blood. At times the actual pH of the fetus was higher than the equilibrated pH and, during the latter part of the first stage of labor, it was lower. The base excess paralleled the

equilibrated pH. There was very little fluctuation of the equilibrated pH and the base excess. At no time was there evidence of biochemical abnormality of the fetus.

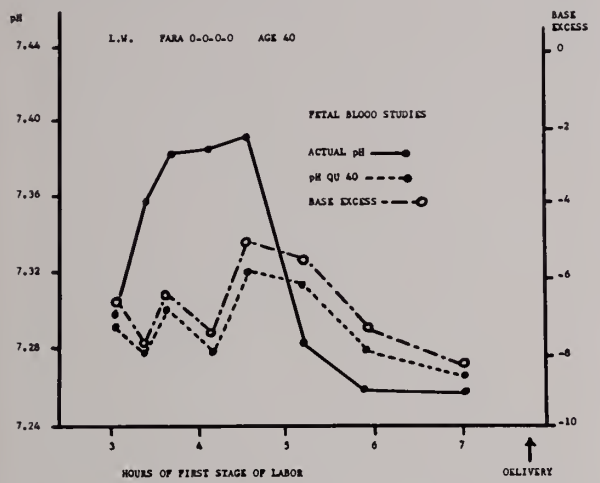


Fig. 5—Complete acid-base studies were obtained on eight occasions during a four-hour period in late first stage of labor. The actual pH, equilibrated pH and base excess of the fetus are presented. There is wide variation of the actual pH with minimal fluctuation of the equilibrated pH and base excess.

Figure 6 shows the actual pH of the fetus as well as the base excess of the patient and the fetus. In this figure it is noted that the base excess of the patient and the fetus paralleled each other rather closely, with the base deficit being less in the patient. This is the usual relationship. As the fetus had a base deficit of significant degree, it might be inferred that it

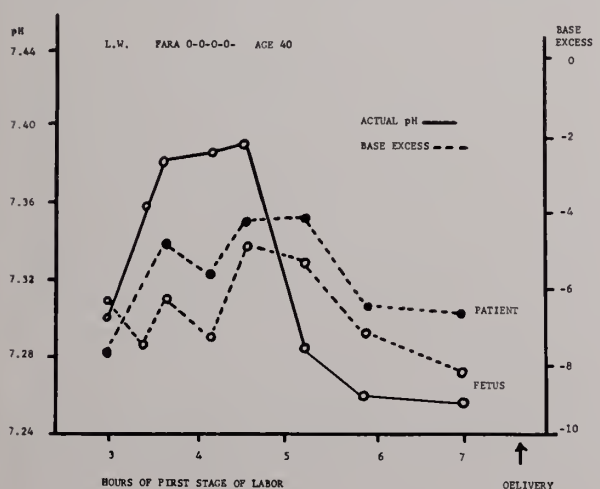


Fig. 6—Base excess of the mother and fetus are presented, showing the fetus to have a greater base deficit than the mother but paralleling that of the latter. The fetal actual pH is also shown.

was in jeopardy. But the fetus was not depressed at birth and the fetal metabolic acidosis was likely passively acquired from the mother.

In Figure 7 the actual pH of the patient and the fetus are plotted as well as the base excess of the fetus. It can be seen that the actual pH of the fetus paralleled that of the mother but was consistently lower.

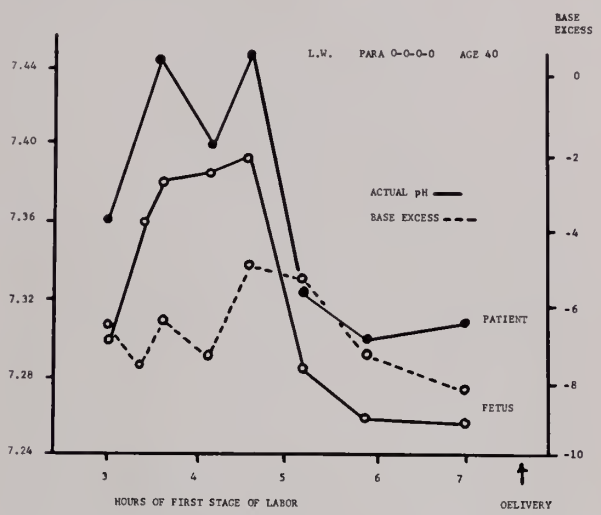


Fig. 7—The actual pH values of the mother and fetus are plotted, demonstrating the wide variations in each. The fetal actual pH is always lower but follows that of the mother. Fetal base excess also shows minimal fluctuation.

Observations

These cases illustrate a number of points regarding fetal-maternal acid-base relationships: (1) there is wide fluctuation of the actual pH of the fetus which bears a definite relationship to that of the mother; (2) the fetal pH is always lower than the maternal pH; (3) the equilibrated pH or base excess more accurately reflects the acid-base status of the infant than the actual pH; and (4) the metabolic parameters of the fetus and mother also parallel each other, with the fetus usually being more acidotic.

Clinical Application

Table 4 outlines the management of the patients with fetuses having metabolic acidosis. In general, if significant fetal acidosis is found together with clinical evidence of distress, the infant should be delivered without delay. If there is no other clinical evidence of fetal distress, acid-base studies should be repeated fre-

quently, the fetal heart rate monitored continually, and parenteral fluids, with sodium bicarbonate if indicated, administered. Provision should be made for immediate delivery.

TABLE 4
Significant Fetal Metabolic Acidosis Management

A.	Clinical Fetal Distress—Delivery
B.	No Clinical Distress
	1. Serial Studies at Frequent Intervals
	2. Close Monitoring of FHR
	3. Parenteral Hydration
	4. Preparation for Immediate Delivery

It has been amply demonstrated that fetal blood studies properly evaluated can minimize unnecessary operative intervention.[3,14,17,21] On the other hand, an occasional infant will be delivered without delay and be salvaged before irreversible damage has resulted. High-risk patients, such as those with diabetes mellitus or toxemia, should of course be monitored closely. Usually labor can be allowed to progress under such a regime. Occasionally, early fetal distress can be diagnosed by fetal acid-base evaluation before other clinical signs appear, and these infants can be saved by prompt operative intervention.

Summary

Fetal blood sampling is a safe, simple and rapid monitoring procedure. An appreciation of the fetal-maternal interrelationships allows for an accurate interpretation of the results obtained. This information, together with clinical evaluation, should reduce perinatal deaths and morbidity and hopefully decrease the number of unnecessary cesarean sections for fetal distress in utero.

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Old age lacks the heavy banquet, the loaded table, the oft-filled cup; therefore it also lacks drunkenness, indigestion and lack of sleep.—Cicero

Reflex Sympathetic Dystrophy

Review of 140 Cases

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THIS REPORT ASSESSES the clinical manifestations and management in 140 cases of reflex sympathetic dystrophy and summarizes some current concepts of pathogenesis. The term "reflex sympathetic dystrophy" has been used to describe disorders of an extremity that are characterized by neurovascular disturbances and dystrophic changes of skin, subcutaneous tissues, bones, and joints and that frequently follow external trauma. In this presentation we have included cases that represent what could have been related or similar and overlapping syndromes, such as Mitchell's causalgia,[1] Sudeck's atrophy,[2] Homans' minor causalgia,[3] Steinbrocker's shoulder-hand syndrome,[4¶] and similar disorders classified by other terms and perhaps presenting minor differences (see Discussion).

Diagnostic Criteria

Our criteria for the diagnosis include: (1) evidence of neurovascular disturbances such as (a) pain, hyperesthesia, and tenderness, and (b) swelling, color and temperature changes of the skin, and hyperhidrosis or dryness; and (2) evidence of dystrophic changes such as (a) a thin, glossy, or atrophic appearance of the skin and subcutaneous tissues, (b) stiffness, decreased range of motion, or fibrous ankylosis of joint and periarticular tissue, and (c) osteoporosis. History of a possible precipitating episode may be significant and helpful in establishing a diagnosis.

Method

The material for this study consisted of the case records of all patients with a diagnosis of reflex sympathetic dystrophy plus those with similar or allied conditions generally considered variants of this disorder who were seen at the Mayo Clinic during the years 1965 and 1966.

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†Mayo Clinic and Mayo Foundation: Section of Physical Medicine and Rehabilitation.
‡Mayo Clinic and Mayo Foundation: Section of Medicine.
¶See page 572.

Review of this material disclosed 140 cases that clearly met the above-listed criteria. Data were collected and analyzed for the series as a whole; then the data on patients with shoulder-hand syndrome were analyzed separately. The shoulder-hand syndrome is characterized by pain or stiffness or both in a shoulder and painful swelling of the homolateral hand, in which neurovascular disturbances and dystrophic changes are apparent. The term "variants" includes causalgias, Sudeck's atrophy, minor causalgia, and similar disorders variously described by other authors using diverse terms which present minor distinctions.

TABLE 1
Age Distribution (140 Cases)

Age, years	Shoulder-hand syndrome (44 cases)		Other variants (96 cases)		Total (140 cases)	
	No.	%	No.	%	No.	%
≧70	13	29.5	9	9.4	22	15.7
60-69	13	29.5	19	19.8	32	22.9
50-59	10	22.7	23	24.0	33	23.6
40-49	8	18.2	22	22.9	30	21.4
30-39	....	....	13	13.5	13	9.3
≦29	....	....	10	10.4	10	7.1

TABLE 2
Precipitating Factors

Factor	Shoulder-hand syndrome (44 cases)		Other variants (96 cases)		Total (140 cases)	
	No.	%	No.	%	No.	%
Soft-tissue trauma*	2	4.5	38	39.6	40	28.6
Fracture	4	9.1	24	25.0	28	20.0
Postoperative condition	4	9.1	19	19.8	23	16.4
Myocardial infarction	12	27.3	....	....	12	8.6
Tendinitis of shoulder	6	13.6	....	....	6	4.3
Degenerative joint disease of cervical spine	3	6.8	....	....	3	2.1
Cerebrovascular disease	3	6.8	....	....	3	2.1
Others	4	9.1	....	....	4	2.9
Unknown	6	13.6	15	15.6	21	15.0

*Includes eight patients with nerve injury.

Observations

Age

Of the 140 patients, 52 were male and 88 female, representing an approximate ratio of two to three. As indicated in Table 1, no patient less than 40 years old had shoulder-hand syndrome, while 23.9% of those with other diagnostic variants were under 40 years of age.

Precipitating Factors

Precipitating factors are listed in Table 2. Sixty-five percent of all patients had had external trauma, fractures, or surgical treatment prior to onset of the disorder. Internal lesions as possible precipitating factors were restricted to the patients with shoulder-hand syndrome. Thus, 27.3% of patients with shoulder-hand syndrome had a myocardial infarction as a precipitating factor. A precipitating factor was not apparent in 15% of the total series.

Delay Interval

The time between the probable precipitating episode and evaluation at the Mayo Clinic averaged 8.8 months (range 0.5 to 74). Fifty per cent of the 140 patients were seen at the Mayo Clinic less than six months after the probable precipitating episode, while 18% were not seen until more than 12 months after such an episode.

Symptoms and Signs

All patients complained of pain which varied in severity and character. Diffuse swelling and decreased range of motion of affected extremities were the next most common findings (in about 86% of cases). Changes in skin color, moisture, temperature, and texture were noted in 61.4%. Hyperesthesia was recorded in only 22.9%. Roentgenograms of affected extremities were taken in 92.2% of the patients, of whom 62% were reported to have osteoporosis (Table 3). Only three patients had a record of Raynaud's phenomenon. Changes in the skin occurred in 72.9% of the patients with other variants but in only 36.4% with shoulder-hand syndrome. Hyperesthesia also was more frequent in other variants (30.2%) than in the shoulder-hand syndrome (6.8%). The differences in symptoms and signs between these two

groups were only minor.

Associated Psychiatric Involvement

Fifty-two patients (37.1%) had a history of psychiatric problems or emotional disturbance prior to onset of the present illness. Twenty-five had formal psychiatric consultations at the Mayo Clinic. The 35 patients not referred for formal psychiatric evaluation during the present illness were thought by their internists at the Mayo Clinic to have psychiatric problems. All were classified as manifesting evidence of psychoneurosis including anxiety-tension state, conversion reaction, or depression. The diagnoses made by the psychiatrists agreed, except for one patient with organic cerebral deterioration and another with a schizophrenic disorder.

Physical Treatment

One hundred twenty-four patients (88.6% of all patients) were referred to the Section of Physical Medicine and Rehabilitation for evaluation and treatment. Forty-nine received physical therapy for less than three days, primarily for the purpose of instructions in a program for home treatment. The others had more than three days of intensive physical therapy and more adequate instructions.

Physical therapeutic measures included the local application of heat, contrast baths, manual massage, normal-range exercises, graded use, occupational therapy and, less often, stretching, relaxation exercises, instruction in posture and gait principles, and use of decompressive devices to reduce swelling.

The most commonly used heating modalities were radiant heat, contrast baths, and whirlpool baths. Only mild heating of tissues was used, as high-intensity or prolonged heating tends to increasing swelling.

Deep stroking and kneading massage was prescribed for most patients. Essentially all had therapeutic exercises. Active and active-assistive normal-range exercises were prescribed for more than 60% of the patients. Re-education, coordination, resistive exercises, or combinations of these measures were used when indicated. Passive exercises were prescribed for fewer than 10%.

On dismissal, 80% of the 75 patients who received physical therapy for more than three days showed improvement.

Other Measures

Sixty-three patients (45%) received injections or surgical treatment for the reflex sympathic dystrophy. Thirty-eight had sympathetic blocks and 15 had local injections of compound F; eight had sympathectomy, and two had neurolysis.

Follow-up Information

The records of 68 patients (48.6%) contained follow-up information. Of these patients, 92% showed or indicated improvement. The time between dismissal and follow-up ranged from 1 to 35 months (average 9.2).

TABLE 3
Principal Symptoms and Signs

	Shoulder-hand syndrome (44 cases)		Other variants (96 cases)		Total (140 cases)	
Symptom or sign	No.	%	No.	%	No.	%
Pain	44	100.0	96	100.0	140	100.0
Swelling	37	84.1	84	87.5	121	86.4
Decreased range of motion	42	95.5	78	81.3	120	85.7
Tenderness	27	61.4	74	77.1	101	72.1
Change in skin*	16	36.4	70	72.9	86	61.4
Hyperesthesia	3	6.8	29	30.2	32	22.9
Osteoporosis	21	53.8†	59	65.6†	80	62.0†

*Includes color, moisture, texture, and vasospasm.
†Percentage of patients who had x-ray examination.

Characteristics of Syndromes

Causalgia

In 1864 Mitchell and co-workers[1] described severe, intractable, peculiar burning pain associated with glossy skin after nerve injury and applied the term "causalgia" to the condition. According to Drucker and co-workers,[5] causalgia is "a burning type of pain not confined to the distribution of a peripheral nerve which occurs after trauma to a major nerve of an extremity and which can be relieved by sympathetic interruption."

Sudeck's Atrophy

In 1900 Sudeck[2] described a condition of an

extremity in which, after trauma to a joint, pain develops and is associated with tenderness, edema, vasomotor disturbances, stiffness of joints, and acute atrophy of bone with characteristic spotty decalcification. Subsequently various names have been applied to the same syndrome: acute atrophy of bone, traumatic angiospasm, chronic traumatic edema, peripheral trophoneurosis, post-traumatic osteoporosis, and reflex nervous dystrophy.[6]

Minor Causalgia

There are patients who complain of pain in the extremities but whose pain is less severe than that of major causalgia and is not necessarily associated with partial or complete injury of a major nerve. It may follow trauma without injury to the nerve or it may not be related to trauma at all but may follow infection or thrombophlebitis. It is characterized by hyperesthesia with sweating and cyanosis. Homans[3] referred to this condition as "minor causalgia" in 1940.

Reflex Sympathetic Dystrophy

"Reflex dystrophy," characterized by atrophic changes of the skin, subcutaneous tissues, and joints, and induced by prolonged neural and circulatory disturbances,[6-10] often due to minor trauma leading to the reflex production of the sympathetic phenomena of rubor or pallor, heat or cold, increased sweating, edema, and pain,[7] and relieved by sympathetic interruption,[8] has been described by many authors. Drucker and co-workers[5] believed that sympathetic dystrophy is fundamentally the same condition as causalgia but that causalgia is initiated by an injury to a mixed peripheral nerve while sympathetic dystrophy may show no such demonstrable injury.

Shoulder-Hand Syndrome

Steinbrocker and co-workers[4,9] reported 42 cases of reflex neurovascular disorders of the upper extremity under the term "shoulder-hand syndrome" and later suggested that clinically and pathogenetically the shoulder-hand syndrome related to an internal lesion is probably identical with reflex dystrophy produced by external trauma.

Stages of Development

Several authors have divided the clinical course into three stages for convenience.[5,9,10]

First Stage

The first stage is characterized by localized persistent pain which is usually aggravated by movement, emotional disturbances, and visual or auditory stimuli. The skin may be hyperesthetic, tender, swollen, and either warm and dry or perspiring. The muscles may be hypertonic. The joints involved may have decreased range of motion owing to periarticular swelling and pain on movement. There is no radiographic evidence of osteoporosis. The interruption of sympathetic pathways may provide good relief of pain at this stage. The disorder may be controlled or improved by adequate therapy; or it may progress to the second stage.

Second Stage

In the second stage the pain and edema may spread proximally for some distance. The skin becomes cool, pale or gray, and often cyanotic and shiny, with atrophic changes. The hair may be scant. Stiffness increases and muscles atrophy. Osteoporosis may be evident in roentgenograms. Interruption of the sympathetic pathway may become less effective in relieving pain, but the condition is generally still amenable to treatment.

Third Stage

The third stage is characterized by progressive atrophy of skin, muscle, bone, and joints. The joints contract, even to the stage of fibrous ankylosis. Osteoporosis becomes diffuse. The pain may be intractable and even more widespread.

Apparent Precipitating Causes

Of the 61 cases of sympathetic dystrophy in the series of Drucker and colleagues,[5] 45 followed fracture, sprain, laceration, and trauma to soft tissue; in only five were no precipitating factors found. Johnson and Pannozzo[11] and Rosen and Graham[12] reported that in about 63% of their patients with shoulder-hand syndrome the onset followed degenerative disease of the cervical spine, cardiovascular dis-

ease, cerebrovascular disease, pulmonary disease, or combinations of these, while in about 10% precipitating factors were unknown.

Osteoporotic Changes

Miller and De Takats[13] expressed the view that the osteoporosis does not occur unless four to eight weeks of continuous collateral hyperemia have been present. It appears as mottled, spotty decalcification in small bones of the feet or hands and in the metaphysis of long bones. After sympathectomy the pain may rapidly subside, but the osteoporosis persists for many months. The incidence of osteoporosis in reflex sympathetic dystrophy has been reported as being 30 to 50%.[5] In our series the incidence was 62%.

Personality

The personality changes found during the painful stage of this disorder have been thought by several investigators[5,14,15] to be secondary to the pain. A significant number of our patients (37.1%) had psychiatric problems, mostly in the category of psychoneurosis.

Holden[8] emphasized psychiatric support in treating patients with sympathetic dystrophy, while De Takats[10] has been disappointed in the psychiatric approach to these problems.

Treatment

There is no entirely satisfactory specific treatment; most authors, however, believe that treatment in the earlier stages is the most effective. Analgesics are generally prescribed to relieve the pain. Various surgical procedures have been described and thought to be helpful, including sympathetic block, sympathectomy, local injection of analgesics or corticosteroids or both, and neurolysis.

Physical Therapy

It seems generally accepted by many investigators that physical therapy should be initiated early, as such therapy immediately after blocking of the sympathetic chain appears to enhance improvement.[13]

In general, we have prescribed physical therapeutic measures, attempting in part to relieve pain and swelling, to maintain or increase the range of motion, to encourage the patient to use actively the involved extremity as tolerated, and to reeducate involved muscles when indicated. Training the patient to continue intensive regular physical therapy at home has been an essential part of our therapeutic approach. In involvement of the lower extremity, an hourly walking schedule beginning with one or two minutes and gradually increasing the time and amount of weight-bearing is prescribed.

Plewes[16] treated 37 patients with Sudeck's atrophy in the hands and observed that conservative measures including heat, elevation, and graded function were effective if initiated within six weeks after the onset of symptoms. Johnson and Pannozzo[11] treated 76 patients who had shoulder-hand syndrome with physical measures alone, and suggested that equally good results may be obtained by physical treatment alone as by sympathetic blocking. It was emphasized that most authorities recommend active exercise following the sympathetic block. With their physical therapeutic program, 53 patients showed good improvement, 10 fair, and two none.

Rosen and Graham[12] reported that the use of cortisone and ACTH in addition to routine physical measures gave the best results for shoulder-hand syndrome—better than intensive physical therapy alone.

Theories of Pathogenesis

The possibility that sympathetic afferents transmit pain has been studied, but the evidence is not conclusive.[2,15] The theory of the internuncial* pool has been offered to explain the continuous sympathetic activity and its spread.[4,5,7] Another theory is that as a result of an "artificial synapse" in a partially damaged peripheral nerve, efferent sympathetic impulses produce painful impulses via afferent fibers.[17] Granit and colleagues[18] presented experimental evidence of cross stimulation between motor and sensory fibers in a cut region of a nerve, or in a crushed region and in a region subjected to moderate mechanical pressure.

*See Test Your Word Score, page 523.

Small unmyelinated C fibers have been traced from the periphery to the medulla and up into the midbrain in cats.[19] Drucker and associates[5] have speculated that the pain in causalgia and causalgic states could be transmitted by the small unmyelinated C fibers, and that increased activity of the C fibers contributes to the intense activity of the internuncial pool. They[5] further proposed a composite concept of the pathogenesis of reflex sympathetic dystrophy, integrating the above-mentioned neurogenic theories: that of the internuncial pool, the "artificial synapse," and the increased activity of C fibers. Cerebral and hypothalamic impulses may affect activity of the internuncial pool.

In addition to cross stimulation through the artificial synapse, there is evidence of release of a diffusible pain substance (neurokinin) from the "artificial synapse" by peripherally directed impulses.[10,15]

Thus the factors considered in the pathogenesis of reflex sympathetic dystrophy at present include (1) cross stimulation and release of pain substance (neurokinin) at an "artificial synapse," (2) increased activity in the internuncial pool in the spinal cord, and (3) increased activity of C fibers as an afferent pathway.

Summary

The term "reflex sympathetic dystrophy" as used herein includes Steinbrocker's shoulder-hand syndrome, Sudeck's atrophy, Mitchell's causalgia, and Homans' minor causalgia. In an analysis of 140 cases of reflex sympathetic dystrophy the following observations were made.

The shoulder-hand syndrome predominated after age 50, the other variants before age 50. Possible precipitating factors were recognized in 85% of cases. Osteoporosis occurred in the affected extremity in 62%. Psychiatric problems or emotional disturbances existed prior to onset of the present illness in 37%. Of those receiving physical therapy for more than three days, 80% showed subjective or objective improvement at dismissal. Of 68 patients followed subsequently, 92% showed improvement.

No single concept of pathogenesis is entirely satisfactory .

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If you would lift me you must be on higher ground.—Emerson



Editorials

Atherosclerosis Obliterans*

THE ROLE and the timing of surgical procedures (lumbar sympathectomy, arterial reconstruction, arterial grafts) remain controversial in the treatment of ischemic limb disease. Proponents of "early" surgery speak of preventing limb loss and improving living conditions of the patients. The non-surgical approach emphasizes the ability of patients to live with symptoms but without surgical intervention.

There is little controversy about the patient with severe ischemic changes (ulcers, gangrene) in the limb. The proponent of early surgery strongly believes that the patient could have been spared this *if only* the surgeon had seen him "earlier." Just how much "earlier" is not clear, however.

A chronic disease, atherosclerosis obliterans is individual to each person in its vagaries, presentations, and outcome. The "natural history" *in the individual is not* usually well documented and probably starts years before the limb is endangered.

Significant serial objective facts are usually lacking, even such simple data as accurate pulse mapping before and after standard exercise. Few offices or hospitals provide facilities for reflex skin-temperature responses, digital plethysmography, standard exercise evaluation of claudication time, or color photography. Hair growth, skin texture, limb girth are not usually recorded. In most patients, this data could be recorded in conjunction with symptoms over months of followup prior to any surgical procedure, if indeed a surgical procedure is needed.

The ease of arteriography and the visual impact of diseased arteries have over-shadowed the "simpler" but more time-consuming tests. Often one suspects that the decision for surgical procedures is an expedient of the angiographic display, the desire to "help the patient," and the inclination of the physician that "there is little else to do" after a trial of drugs.

It is my belief that patient education and specific reconditioning programs are sorely needed. Treatment of this chronic disease requires constant professional reinforcement so that the patient (1) attains a satisfactory weight, (2) abstains from tobacco products, (3) develops superb skin hygiene and foot care, (4) employs proper clothes, hands and footwear, (5) engages in limb reconditioning as well as general reconditioning by selected exercises, and (6) appreciates the chronicity of the problem. Complete patient evaluation should evaluate not only the medical situation but also the socioeconomic background of the patient and the physical demands of work and leisure. This education will be supportive if a surgical procedure is performed.

Lack of physician time is a strong barrier to this type of evaluation and support program. The role of paramedical personnel and vascular diagnostic clinics should be re-evaluated.

Pontification is an easy matter. Implementation is not. Yet I strongly believe that the medical-surgical treatment of patients with atherosclerosis obliterans must be placed on a sturdy base. More sophisticated diagnostic technique will not replace a solid program of patient involvement in his own care.

Jerome Grismer, M.D.
Minneapolis, Minnesota

*See page 487.

Doctor, after all we've been through together...

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amebiasis
anthrax
bacillary dysentery
bartonellosis
bronchitis
bronchopulmonary infection
brucellosis
chancroid
diphtheria
endocarditis
genitourinary infections
gonorrhea
granuloma inguinale
listeriosis
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Precautions: Nonsusceptible organisms may overgrow; treat superinfection appropriately. Tetracycline may form a stable calcium complex in bone-forming tissue and may cause dental staining during tooth development (last half of pregnancy, neonatal period, infancy, early childhood).
Adverse Reactions: *Gastrointestinal*—anorexia, nausea, vomiting, diarrhea, stomatitis, glossitis, enterocolitis, pruritus ani. *Skin*—maculopapular and erythematous rashes; exfoliative dermatitis; photosensitivity; onycholysis, nail discoloration. *Kidney*—dose-related rise in BUN. *Hypersensitivity reactions*—urticaria, angioneurotic edema, anaphylaxis. *Intracranial*—bulging fontanels in young infants. *Teeth*—yellow-brown staining; enamel hypoplasia. *Blood*—anemia, thrombocytopenic purpura, neutropenia, eosinophilia. *Liver*—cholestasis at high dosage. Upon adverse reaction, stop medication and treat appropriately.

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Thrombocytosis*

"Decreased platelets" or "platelets less than 100,000" on a laboratory report have historically been a red flag to the physician. Reports indicating thrombocytosis, on the other hand, are less alarming, unless levels greater than 1,000,000 are encountered, at which point thrombotic, or less frequently, hemorrhagic episodes may be anticipated.[1] Thrombocytosis is expected in post-splenectomy, post-surgical, and post-partum states. Except in post-splenectomy, levels greater than 1,000,000 do not frequently obtain. Other causes of non-symptomatic thrombocytosis include chronic bacterial infections, rheumatoid arthritis, acute or chronic blood loss, myocardial infarction, parenchymal liver disease, tuberculosis, and Hodgkin's disease. Monitoring the platelet count has also been suggested as a useful tool in following the activity of granulomatous and ulcerative colitis, in that an increased count appears to reflect recrudesence.[2] Levels greater than 1,000,000 are most frequently seen in the thrombocythemias of the myeloproliferative syndrome.

Prior to 1964, only scattered reports in the literature had associated thrombocytosis with malignant states. In 1964 Levin and Conley[4] made the association more definite. Of 82 patients with thrombocytosis, 31 had malignant disease, comprising the largest single group; of the 31 cases, the most common tumors were of the stomach (7), colon (6), and lung (5). Levels greater than 1,000,000 were seen in two cases of ovarian malignancy and in one case of retinoblastoma. Involvement of the bone marrow did not appear to be a factor in inducing the thrombocytosis.

The current material presented by Silvis et al.[5] is from a much larger series; 339 cases of thrombocytosis were drawn from 12,557 admissions over a period of one year at the Veterans Hospital, Minneapolis, with the records of 322 available for study. Of these, 206 patients had malignant disease, or roughly two out of three, which would appear to be highly significant. Carcinomas of the lung, colon, and stomach again headed the list, although in a different order from that reported in the earlier series (lung 68; stomach and colon 32). This larger series might be expected to be more representative than that of Levin and Conley and again dramatizes the serious import of this laboratory finding.

The stimulus to thrombocytosis remains conjectural. There is presently good evidence for the existence of a specific thrombopoietin[6,7] which appears to be distinct from erythropoietin or leukopoietin. DeGabriele and Penington[8] have recently suggested a feedback mechanism in the release of thrombopoietin in that infusions of viable platelets lead to its inactivation or removal in experimental models.

Inasmuch as thrombocytosis may follow tissue damage of all kinds, thrombopoietin may have a generalized distribution paralleling that of factors in tissue juice which promote local hemostasis. Assuming a tissue origin of thrombopoietin, it is tempting to speculate on the possibility that malignant tumors may elaborate a thrombopoietin-like substance. The aberrant elaboration of hormone-like substances by non-endocrine tumors has been well documented.[9] Extracts from tumors, notably of the lung or the gastrointestinal tract, may in the future yield potent thrombopoietic fractions in cases known to be associated with significant thrombocytosis. Such fractions may be of assistance in further characterizing release mechanisms in other non-tumorous conditions. In addition, such hypothetical fractions could prove clinically useful in the therapy of otherwise resistant and life-threatening thrombocytopenias.

Therapeutic measures are indicated in patients with levels greater than 1,000,000 and in patients who occasionally become symptomatic at lower levels, irrespective of cause. Radioactive phosphorus and alkylating agents (Busulfan, Myleran) have proved effective in lowering platelet levels, but require days to act. In 1966 Colman[10] described an excellent method of reducing blood platelet levels in a matter of hours. The process, termed thrombocytopheresis, involves the drawing of seven to nine units of blood, and reinfusion following dif-

*Silvis, S. E., Turkbas, N., Swaim, W. R. and Doscherholmen, A.: Thrombocytosis: A Clinical Evaluation. Minnesota Med 52:1603, 1969.



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ferential centrifugation. It is, however, rather cumbersome and, because rebound thrombocytosis may be dangerous, alkylating agents may be necessary for maintenance. More recently Rodriguez-Erdmann et al.[11] adopted a somewhat different approach to the problem of symptomatic thrombocytosis; they used dipyridamole, a drug said to have an anti-adhesive effect on platelets, in the therapy of mesenteric thrombosis related to post-splenectomy thrombocytosis (over 1,000,000) in a patient with polycythemia vera. Platelet adhesiveness was significantly reduced and rapid recovery followed. Simultaneous and sequential treatment with an alkylating agent (Chlorambucil) was effective both in lowering the platelet count and in maintaining the lower count. Thus, a pharmacological approach by reducing platelet adhesiveness eliminated the need for the more tedious thrombocytopheresis in the acute symptomatic phase of the thrombocytotic state.

References may be secured from the author or the reprints.

Patrick C. J. Ward, M.D.
Minneapolis, Minnesota

Pulmonary Function Studies

THE AVAILABILITY of clinically oriented pulmonary function testing has unveiled an exciting chapter in the diagnosis and treatment of patients with pulmonary problems. Understanding and utilization of available testing procedures has led to important advances in the physiologic understanding of respiratory failure. Formerly we were dependent upon determination of anatomic or bacteriologic pulmonary alterations; but now the third dimension of functional capability has been added.

Most of us are familiar with some of the multitudinous tests that may demonstrate abnormalities in ventilation, diffusion, and blood gases. Many physicians now determine timed vital capacity as a routine office screening procedure which, very simply, may demonstrate the presence or absence of restrictive or obstructive ventilatory problems. The more complicated tests of ventilation, diffusion and blood gas levels, however, remain as hospital procedures.

Though the value of blood gas analysis in patients with acute respiratory failure is emphasized*, not every patient requires complete evaluation. We, as clinicians who are familiar with the patient and understand the diagnostic or therapeutic problems, must learn to select the particular tests which would be most useful in evaluation of the pulmonary problem in order to keep expense at a minimum as well as utilizing trained personnel to the fullest.

Every physician practising in hospitals of any size or in any location should have the trained technical staff and enough equipment to perform and interpret ventilation tests. The more sophisticated tests of diffusion and blood gas levels require more trained personnel than are universally available and probably should be left to regional centers.

All patients with acute or chronic pulmonary insufficiency or impairment and with or without cardiac complications will benefit from selective pulmonary function testing. It behooves all of us to become more familiar with the unlimited potentialities.

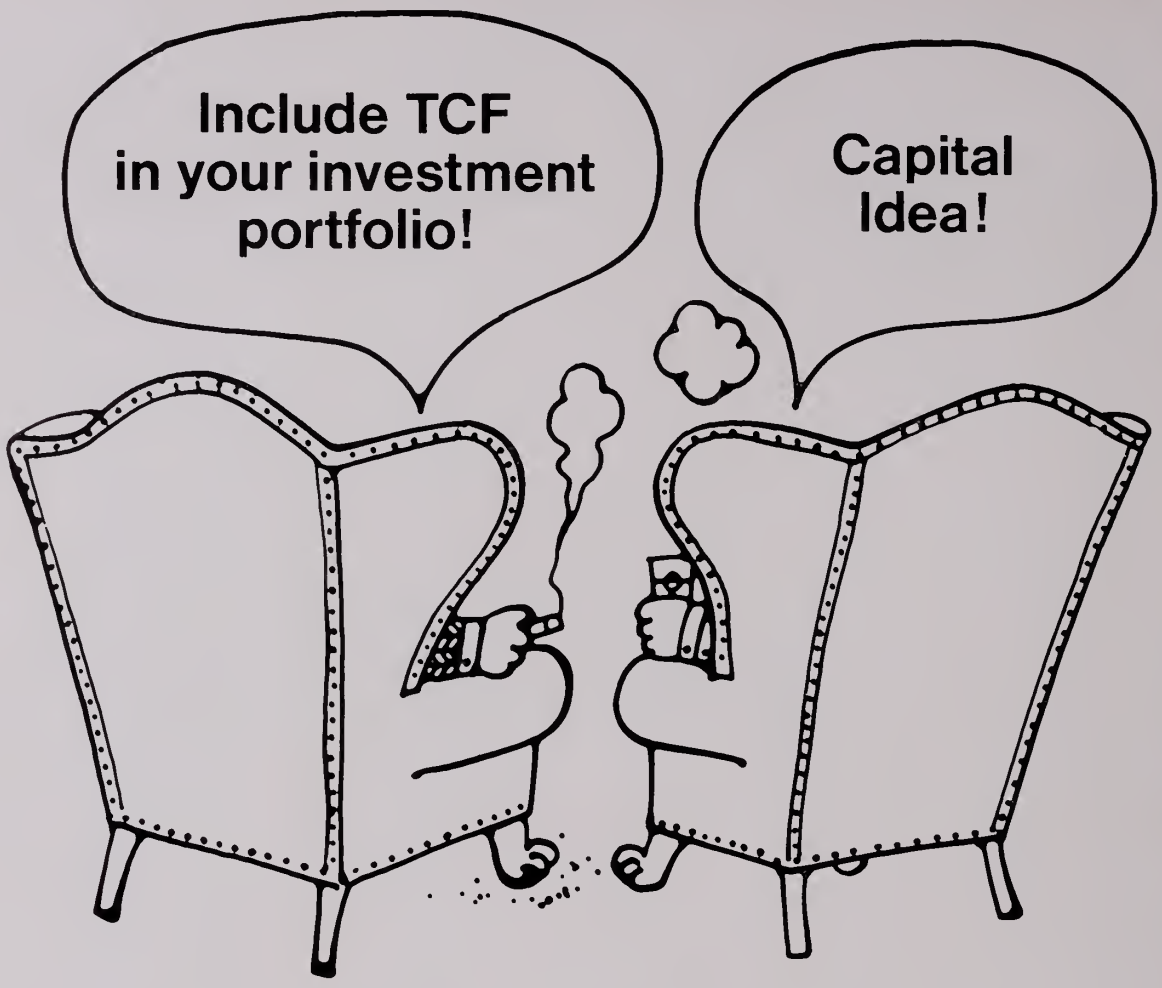
Sumner S. Cohen, M.D.
Minneapolis, Minnesota

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Life

For most of us, life is what we make it, but for the pedestrian, it's if he makes it.—Judge



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Giardia Lamblia*

Physicians who have had Giardia lamblia infestation rarely doubt its pathogenicity. The sudden onset of abdominal pain and diarrhea often suggests malignant gastrointestinal disease. If steatorrhea is present this certainly makes the physician consider carcinoma of the pancreas a likely possibility. The article by Mears and Zinneman is helpful in directing our attention toward this potential pathogen. The organism is highly infective, but in healthy adults the symptoms and the infestation usually subside spontaneously within six weeks. It is obvious from various reported cases that it may produce persistent and significant morphologic and functional changes in the small intestine.

Mucosal invasion has been demonstrated, but the number of trophozoites seen in the subepithelial space seems too small to account for the entire symptom complex. We know that an isolated and reversible lactase deficiency can occur as a result of Giardia infestation; we have personally observed, and it has been amply recorded in the literature, a morphologic alteration in the jejunal mucosa with severe blunting and thickening of the villi and infiltration of the lamina propria. These mucosal changes resemble those seen in nontropical sprue, but the epithelial cells usually remain normal in Giardia infestation.

The mechanism by which the protozoan produces diarrhea with or without steatorrhea is not clear. The vast numbers of trophozoites present in the intestinal tract lend support to the early thought that the trophozoite produces a mechanical blockage to transport of water and nutrients across the cell membrane. Estimates of the number of cysts in a single specimen of stool have ranged up to 14,000,000,000, the average being 300,000,000. Reversion of the abnormal morphology, cessation of diarrhea and steatorrhea, and disappearance of cysts from the stool after treatment with quinacrine (Atabrine) seem ample evidence of the pathogenicity of this parasite.

Examination of the stool for ova and parasites is an important part of the evaluation of anyone with acute diarrhea. Repeated examinations of stool may be necessary and should be carried out if one is suspicious of Giardia infestation, since the cyst, the common form seen on such examination, is produced intermittently in the intestine and appears in showers in the stool at various times.

James R. McPherson, M.D.
Rochester, Minnesota

*Mears, Thomas, and Zinneman, H. H., Giardia Lamblia as Parasite in Humans. Minnesota Med 52:1107, 1969.

Test Your Word Score

Plethysmography—*the recording of changes in measurement of body parts as modified by the circulation of the blood* (Page 487).

Geniculate Arteries—*superior, middle and inferior provide collateral circulation if popliteal is obstructed* (Page 489).

Trophic—*pertaining to nutrition* (Page 491).

Xerostomia—*dryness of the mouth due to lack of natural secretion* (Page 495).

Sialorrhea—*salivation* (Page 496).

Grampians—*a mountain range in Scotland, forming a natural boundary between the Scottish Highlands and Lowlands* (Page 500).

Internuncial—*acting as a medium between two organs* (Page 511).

Hypochromic—*marked by abnormal decrease in the hemoglobin content of the erythrocytes* (Page 566).

Dysarthria—*disorder of articulation* (Page 569).

You May Be Right

Antibiotic Sensitivity Pattern

Inoculum size is a significant variable in any susceptibility test which should be rigidly controlled. The mere presence of a zone of inhibition is not necessarily synonymous with susceptibility. Examination of the interpretative chart in Dr. Matsen's paper* illustrates that substantial zones of inhibition may still be indicative of resistance, depending on the antibiotic tested.

The literature is unfortunately filled with too many antibiotic disc sensitivity studies, such as that of Dexter and Bates† which are invalid and impossible to interpret because of the absence of standardization of inoculum, agar (type not stated), and interpretative criteria of zone diameters of inhibition. The advent of the computer has simply facilitated the collection and retrieval of such invalid data.

John A. Washington II, M.D.
Rochester, Minnesota

*Minnesota Med. 52:1499, September, 1969.
†Minnesota Med. 53:205, February, 1970.

A great deal of work has been done by many competent investigators in the field of antibiotic sensitivity testing. Perhaps the best known in this country have been Dr. William Kirby and Dr. John C. Sherris of the University of Washington. These two physicians have been instrumental in developing a standardized method of disc sensitivity testing which, by extensive testing here at the University of Minnesota, has been shown to be reproducible and accurate. It is my feeling that such a method, well standardized and carefully executed, is as accurate as dilution testing.

Disc testing, using non-standardized inocula and disregarding careful zone size interpretation, on the contrary, is invalid in my estimation.

As both a practicing pediatrician and as the physician in charge of the Diagnostic Microbiology Laboratory at the University of Minnesota, I would urge MINNESOTA MEDICINE to encourage the use of the Kirby-Bauer-Sherris method of disc sensitivity testing in the laboratories throughout Minnesota. Ample evidence exists from the literature and from the World Health Organization Expert Committee to substantiate this recommendation for a standardized use of the single high-potency disc technique.

John M. Matsen, M.D.
Minneapolis, Minn.

*Assistant Professor of Laboratory Medicine & Pediatrics and Director, Diagnostic Microbiology Laboratories, University of Minnesota.

Nobody

Who is wise? He that learns from everyone.
Who is powerful? He that governs his passions.
Who is rich? He that is content.
Who is that? Nobody.—Benjamin Franklin

You May Be Right

(Continued)

The article in reference was accepted for publication *October 1968*. This date preceded the general acceptance of the K & B methodology. At the time data was being "retrieved" no "standardized" disc antibiotic sensitivity test had received general acceptance. Therefore, material presented was done by a "standardized" technique developed in this laboratory. *Editorial brevity* dictated the omission of relative data.

The K & B method is a good standardized procedure, but this does not mean it is the only reliable one. Its value lies in general acceptance which hopefully will result in a uniform interpretation of laboratory data.

Our methodology has been developed and used over the last seven years and was based in part upon the recommendations of the W.H.O. In its development, we have used other bioassays (tube dilutions, S.I. levels, etc.) for verification of its interpretation. Since all bioassays have limitations, clinical follow-up has been done on a number of cases. In general, correlation has been good.

As of December 1969, we have "converted" to the K & B method. Technical efficacy did not permit an earlier change. Some differences have been observed but it is not possible, at this time, to say that they are significant.

In our limited experience with the K & B method we have observed the following.

1. Difficulty in reading "susceptibility" to sulfa drugs. We are not in accord with K & B recommendations on interpretation. Correlative tube tests have verified our observations.
2. 150 mm. plates are difficult to handle.

Henry A. Bates, Ph.D.*
Minneapolis, Minnesota

*Director Research Laboratory, Swedish and St. Barnabas Hospitals.

Stubborn

The patient thought he was dead. His psychiatrist had him stand before a mirror and repeat many times, "Dead men don't bleed."

Then he stuck a pin in the patient's finger and made it bleed a little.

"See now?" the doctor said triumphantly.

"Yes, I see now," the patient replied, "dead men do bleed."*

*Maxwell Droke: The Speaker's Handbook of Humor.

Erratum

Please refer to my article on Pregnancy Tests published in the Laboratory Medicine Section of the March, 1970 issue. In the second column, third line, is an important numerical error. The sentence reading, "During the Menstrual cycle the urinary excretion of pituitary gonadotrophic hormone is at its peak (0.1-4.1 I.U./ml.) during the time of ovulation", is incorrect. The numbers in parenthesis should be changed to read correctly, *0.1-0.4 I.U./ml.*

Charles A. Horwitz, M.D.
Minneapolis, Minnesota



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The Editor's Soliloquy

Physician or Technician

He Who Would Desire Change*

MANY EXCELLENT technical operators have been produced in experimental laboratories from high school graduates. These technicians have mastered the steps of medical and surgical procedures and know how to perform well at the direction of their mentors. Nurses and others have learned to do accurate laboratory routines and execute the infinitely precise details of an intensive care or cardiac recovery room in accordance with the directions of a knowledgeable physician; and European obstetricians have long used midwives to perform the tedious preliminaries of a normal delivery.

They absorb instruction and do highly creditable and responsible work, thus relieving the doctor to engage his valuable time and trained mind in more challenging problems.

The glory of these dedicated employees is unsung in the annals of medical history. They simply work a 40-hour week, collect their bi-monthly check and receive their pay raises in accordance with their tenure; their role in medicine is not that of the leader—they follow instructions. Such is the character of a technician.

The doctor's long and arduous working hours do not fit into a convenient schedule and his monetary reward is no more than commensurate with the value of his service to his patient and to the community. His capacity for infallible decision and judgment must be tempered to the quality of the finest steel through diligent study and adequate training in the basic sciences, metabolic processes, and their potential pathology. He must be capable of meticulous evaluation of abnormal physiologic signs from hour to hour; he must recognize almost instinctively the surgical risks and the medical alternatives thereto of a patient in or out of physical or chemical balance.

Such is the character of the physician!

The categorical distinction between the technician and the physician lies in the magnitude of the doctor's sphere, derived from the twin disciplines: the scientific and the humanistic.

Only a serious study of the liberal arts, time, and maturation, can furnish the broader outlook and deeper insight so invaluable and indispensable to a doctor dealing with human nature as well as diseased bodies. It is the extra-dimensionality that Medicine must not forfeit in quest of earlier specialization. Change is ubiquitous and perennial; but let us not be under the illusion that change always represents progress. If we prefer to distort scientific training by elimination of the humanities from medical education in order to produce younger but narrower specialists, we had better keep one foot tentatively poised in the stirrup, for then we may have to retreat.

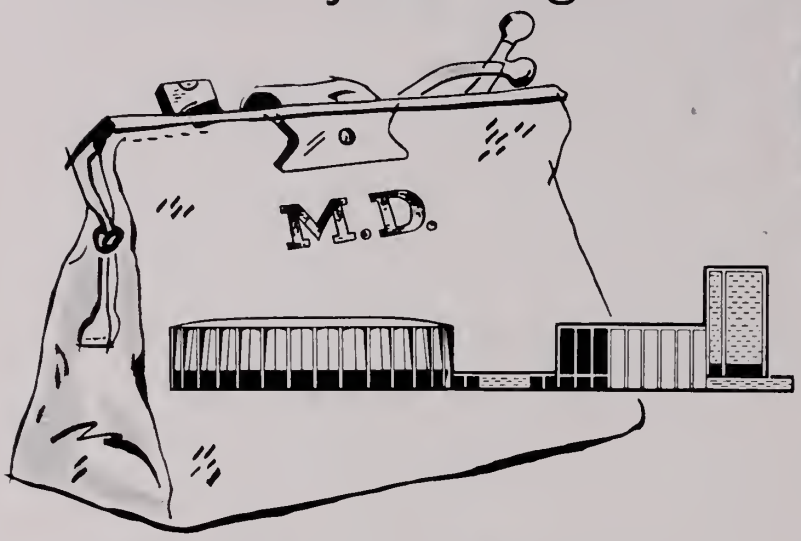
Granted, however, that some change may be desirable, it would seem unnecessary to start a revolution in medical education in order to rectify a few current teachings.*

Carl O. Rice, M.D.

*Turkish proverb: "He who would desire change had better have one foot in the stirrup."

Old Doc Hess says: In order to make your writing palatable, use oil and vinegar to season.

here is your bag in . . .



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Curbstone Consultation

SHALLOW RESPIRATORY SYNDROME

QUESTION: Can you give a typical case report of the "Shallow Respiratory Syndrome"?

ANSWER: A 73-year-old male had experienced progressive dyspnea for the preceding 12 months, not present at rest but precipitated by exercise and severe enough to restrict the patient's activities. Except for a non-productive minimal cough, cardiopulmonary symptoms were absent; there was no orthopnea, weight loss, or chest pain.

The patient had had "pneumonia" twice about eight or nine years previously without known residuals; other than noting occasional vertigo, the systems review was non-contributory.

The physical examination showed a rather well-preserved, elderly white male with respirations of 20 to 24 per minute. The blood pressure was 132/88 and the pulse regular (84 to 88 per minute). The accessory muscles of respiration were being utilized only slightly. The chest diameter was increased to a minimal degree in the anteroposterior plane. As indicated by percussion, the diaphragms moved moderately well. Breath sounds were slightly distant but no rales were audible, even after cough. The heart tones were regular and distant; murmurs were absent. The pulses in the lower extremities were weak. All remaining physical features were non-contributory.

The chest x-rays indicated a lung volume that was thought to be enlarged with a normal-sized heart. There was a faint but definite shadow in the left second anterior interspace. The hilar vessels did not appear unusual. There were no areas of blebs.

An electrocardiogram demonstrated a normal axis and no other abnormality. Circulation time and venous pressure were also within normal range.

Treatment with bronchodilators, expectorants, and other supportive medical measures, after a presumptive diagnosis of "pulmonary emphysema," did not alleviate the dyspnea.

Pulmonary function tests were undertaken and essential studies interpreted as follows.

The ventilatory and the lung mechanics tests were normal except for minimal slowing of the mid-maximum flow, which suggested mild obstructive bronchial disease. However, the maximum voluntary ventilation, formerly "the maximum breathing capacity," was within predicted normal limits, indicating no significant obstructive disease. The residual volume was 42% of the total lung capacity—a normal ratio and lung capacity.

The major findings were shallow rapid respiration and abnormal arterial blood gas levels (Chart). The steady state carbon monoxide diffusion was 17 ml/mm/Hg/minute—a low normal value.

From these studies the interpretation was "shallow respiration syndrome." Rapid shallow respirations result in hypoxemia and low arterial hypoxemia, and also in low arterial pCO_2 (hyperventilation) because of localized poor alveolar ventilation. The high alveolar CO_2 levels are over-compensated in the other portions of the lung, but the hypoxemia cannot be so compensated (the shape of the hemoglobin dissociation curve). As a result the chronic hypoxemia precipitates dyspnea.

If the patient continues this shallow respiration during exercise, hypoxemia remains. However, by proper breathing techniques the hypoxemia can be abolished although hyperventilation remains.

The lesion may be in the central nervous system or its reflex channels. Cerebral vascular insufficiency may be an etiologic basis.

The other causes of dyspnea and hypoxemia must be considered. Multiple pulmonary emboli may be one such problem, but this seems unlikely in this patient in view of the entire evaluation.

Treatment is mainly related to re-education in breathing patterns.

Jerome Grismer, M.D.
Minneapolis, Minnesota

A Trio of Female Centenarians

(Continued from Page 500)

tuous dinner of roast turkey, plum pudding, and champagne, a special indulgence she wisely reserved for birthdays only.

In her versatility of interests, her enthusiasm for living, and particularly her wholesome, never morbid orientation on life, Miss Plunket resembled her sister centenarians, Lady Smith and Mary Elizabeth Haldane. Someone who knew her well during her eleventh decade said of her:

"Her mind is so alert, her interest in current events so keen, her talk so bright, animated and coherent, her sense of humor so unfailing, that she completely belies her enormous age. She has the newspapers read to her regularly, and follows intelligently all the world's happenings. . . . All through life she has preserved an easy mind, and banishes worry with slumber. She subscribes to the simple creed that all good things come from the Almighty, and that when perchance a bad thing comes her way, it has been sent for her good. . . . For length of days, if not for variety of richness and experience, the Honorable Katherine Plunket is easily the most wonderful of the group of centenarians whose careers are narrated in this volume. She completed her fifth score more than ten years ago (1930), and with invincible spirit still looks wistfully forward."

Now, though strangers to one another, what qualities did this "female trio" share in common besides their magnificent age? First, they were adepts at living life to the full through the catalyst of their engrossing interest in it and their capacity to participate in it. Second, they ever remained in the foreground; they never retired to the background. Unlike far too many aged individuals who dwell both *in* and *on* the past, to these splendid women the past was vital only as it represented prologue to an engaging present and an enticing future.

With acknowledgments to and quotations from W. Forbes Gray: Five Score, 1931.

Note: We assume that Miss Plunket is no longer living in this year of 1969; but efforts to learn the date of her demise have been fruitless.

The Viewing Box

Large Marginal Ulcers Following Partial Gastrectomy

THE PATIENT is a 70-year-old male with upper abdominal pain and recent onset of tarry stools. Thirty years previously, an antral exclusion operation had been performed for duodenal ulcer disease.

An upper gastrointestinal series (Figure) reveals two large marginal ulcers (arrows) on opposite sides of the stoma between the stomach and jejunum. The efferent loop is somewhat dilated: the afferent loop fills retrograde through the duodenum into the antral stump (arrow head).

What's your diagnosis? (See next page.)



Figure—Arrows point to the two marginal ulcers.

Diagnosis: Retained gastric antrum producing marginal ulcers: An iatrogenic syndrome.

Antral exclusion operations with end-to-side gastrojejunostomies were performed until the 1940's when a high incidence of recurrent ulcers following this operation was appreciated.

The hormone gastrin is produced by the mucosal cells of the gastric antrum. Gastrin stimulates the parietal cells of the body and fundus of the stomach to produce acid. Normally the acid contents of the stomach suppress much of this gastrin production; however, after an antral exclusion procedure, the antrum is in an alkaline environment from reflux of duodenal contents. This serves as a continuous stimulus to the production of gastrin which, in turn, results in high acid production by the body and fundus of the stomach.

The mechanism of ulcer formation is similar to that of Zollinger-Ellison syndrome, whereby excess gastrin is produced by a pancreatic tumor. Retained gastric antrum should also be considered as a possible etiology of excess gastrin production and large marginal ulcers.

In this patient, 5 cm. of retained gastric antrum were resected. Two huge penetrating marginal ulcers were removed and a new Billroth II anastomosis and vagotomy was done. The dilatation of the efferent loop was secondary to inflammatory reaction produced by the penetrating ulcers. The patient has done well since the procedure.

Leonard H. Levitan, M.D.*
St. Paul, Minnesota

*Department of Radiology, St. Luke's Hospital.

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Ugliness

It was not until I had attended a few post-mortems that I realized that even the ugliest human exteriors may contain the most beautiful viscera, and was able to console myself for the facial drabness of my neighbors in omnibuses by dissecting them in my imagination.—J. B. S. Haldane

---

Sitting

We sit at breakfast, we sit on the train on the way to work, we sit at work, we sit at lunch, we sit all afternoon . . . a hodgepodge of sagging livers, sinking gall bladders, drooping stomachs, compressed intestines and squashed pelvic organs.—Dr. John Button, Jr.

Obesity

The general creased a little in the middle to signify he was bowing.—Negley Farson



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References: 1. Gardner, H. L.: J. Miss. M.A. 8:529, 1967. 2. Parter, P. S., and Lyle, J. S.: Arch. Dermat. 93:402, 1966. 3. Walsh, H.; Hildebrandt, R. J., and Prystawsky, H.: Am. J. Obst. & Gynec. 93:904, 1965. 4. Vaginitis and the Pill: J.A.M.A. 196:731, 1966. 5. Guerriera, W. F.: Sauth. M.J. 56:390, 1963. 6. Seelig, M. S.: Am. J. Med. 40:887, 1966. 7. To-day's Drugs, New York, Grune & Stratton, Inc., 1965, p. 316. 8. Gray, L. A., and Barnes, M. L.: Am. J. Obst. & Gynec. 92:125, 1965. 9. Salerna, L. J.; Ortiz, G., and Turkel, V.: Vaginitis: A Diagnastic and Therapeutic Apprаach, Scientific Exhibit, presented at the 115th Annual A.M.A. Canventian, Chicaga, Illinais, June 1966. 10. Walsh, J. C.; Sheffery, J. B., and Wilsan, T. A.: Med. Ann. D.C. 37:358, 1968. 11. Nugent, F. B., and Myers, J. E.: Pennsylvania Med. 69:44, 1966.

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Dermatology

Keratoses

Arsenical

KERATOSES FOLLOWING the ingestion of inorganic arsenic appear as discrete, warty lesions usually on the palms, fingers, and soles. They are generally symmetric and surmounted by a small, black shiny peg of keratin. Fissuring is common. Keratoses following the ingestion of organic arsenic are rare. Keratoses may develop within a month or as long as 30 years later. Once the lesions appear they usually persist. Twenty percent of the cases eventuate in carcinoma even though there is no further ingestion of arsenic. There seems to be an individual susceptibility or tolerance to arsenic. Some patients can take the drug for years with only mild pigmentation and keratoses; others develop keratoses and carcinomas followed by metastasis and death with only small amounts of the medication.

Treatment for arsenical keratoses is unsatisfactory. When carcinoma develops, surgical excision is the method of choice. If carcinoma is present on a digit or on the palms and soles, amputation may be necessary.

Seborrheic (Verruca Senilis)

Seborrheic keratoses, sometimes confused with actinic keratoses, are not precancerous; they are more superficial and softer than the actinic ones. Us-



Fig. 1—Multiple seborrheic keratoses on the back.

ually, seborrheic keratoses are multiple and raised slightly above the surface of the surrounding skin. Their color varies from light brown to almost black; they usually occur on the face, back, and chest. Removal of the loosely attached greasy crusts shows a raw pulpy base. They begin in middle age; basal cell carcinoma develops in 1 or 2%. Seborrheic keratoses should not be treated with x-rays or radium but destroyed by cauterization or desiccation.

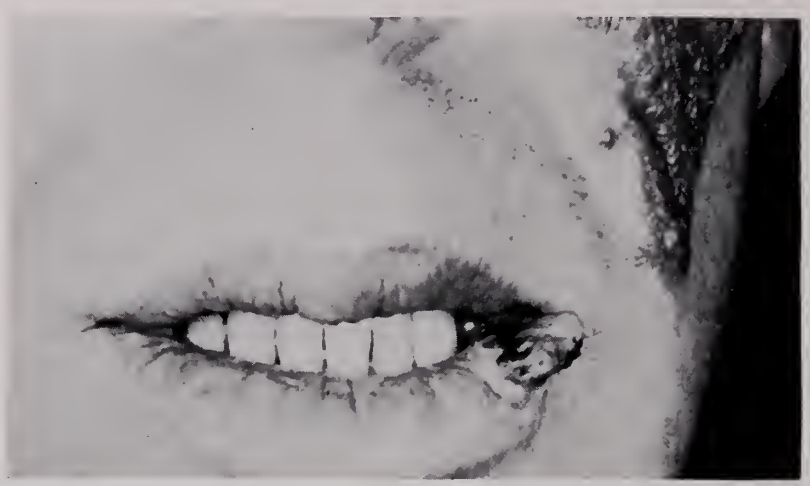


Fig. 2—Cutaneous horn of the lip. Squamous cell carcinoma develops frequently.

Actinic Type

People exposed to sun and wind for many years develop these lesions on exposed parts, especially the hands and face. Actinic keratoses may be single or multiple; they are usually dark brown or black; their surface is uneven, superficially ulcerated, and bleeds easily. They are firmer, more discrete, and more raised from the surface of the skin than seborrheic keratoses. In 20 to 25% of the cases squamous cell carcinoma develops. Actinic keratoses are radioresistant and should be destroyed by cauterization or desiccation.

Cutaneous Horn

These lesions are rare and may resemble similar growths in lower animals. The majority develop from actinic keratoses; carcinomatous changes occur frequently. Cutaneous horns are similar to actinic keratoses except that there is an excessive development of keratotic material. They may be cylindric, straight or twisted. They occur usually on the scalp and face; sometimes other areas are affected. The color varies from light brown to black; they may be short or several inches long.

Treatment is the same as for actinic keratosis. If the horn is small and shows no evidence of carcinoma destroy it by cauterization or desiccation. Excise large ones, especially if the clinical features suggest malignancy (rapid growth, ulceration, and so forth).

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Minneapolis, Minnesota

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Reprint requests to 538 Southdale Medical Building, Minneapolis, Minnesota 55435.

Case Report

Placenta Previa Accreta

PETER J. BARTZEN, M.D.
Duluth, Minnesota
GERALD L. JURGENS, M.D.
St. Paul, Minnesota

THE RARITY of placenta previa accreta warrants the report of a case by anyone unfortunate enough to have experience with this potential killer. In an excellent review of the subject in 1961 Friesen[1] collected 52 cases from the literature and then added 40 cases in 1968.[2] The incidence of placenta accreta varies from zero in 20,000 deliveries at Johns Hopkins to one in less than 2,000 at Boston City Hospital; it is five times as common as fundal accreta. Previous trauma, especially low cervical cesarean section, is said to predispose to the condition. Maternal mortality is 6.6% if the problem is treated with hysterectomy and 64.7% if the uterus is preserved. The usual difficult decision between radical and conservative therapy arose in the following case.

Case Report

A 31-year-old white female, with two living children, was first seen for prenatal care at ten weeks' gestation. Her last menstrual period had been July 17, 1967; the expected date of confinement, April 24, 1968. There had been daily spotting since the first missed menses. A Gravindex test was positive and the uterus was of appropriate size for the stated duration of gestation. Past obstetric history included a normal vaginal delivery of an eight-pound, thirteen-ounce infant at term in 1962; a low cervical cesarean section in another institution at 30 weeks' gestation for placenta previa in 1964; a left salpingo-oophorectomy for ruptured tubal pregnancy in 1964; and a normal vaginal delivery at 38 weeks' gestation of a normal eight-pound, seven-ounce infant in 1967.

At 16 weeks' gestation in this pregnancy the patient required hospitalization and a single blood transfusion because of painless postcoital bleeding. A second episode of bleeding that required hospitalization but no transfusion occurred at 29 weeks. This bleeding subsided spontaneously. The third and final hospitalization for bleeding occurred at 34 weeks.

Bleeding continued in small amounts over the first five days after admission. Three units of blood were necessary to keep the hemoglobin at the 11.3 grams % level. Blood pressure and fetal heart tones were stable during this interval. On March 19, 1968, at nearly 35 weeks' gestation, sudden sharp supra-pubic pain developed followed by profuse vaginal bleeding. An emergency abdominal delivery was undertaken without double setup and before the onset of shock.

The Caesarean Operation

At surgery the bladder flap was not identified because of a huge nest of dilated vessels covering the entire lower one-third of the visible uterine corpus. Excessive dextrorotation of the uterus was present. A vertical incision was made, one-half in the corpus and one-half transecting the cervical portion of the placenta.

A five-pound, ten-ounce normal female infant was quickly delivered feet first. Examination found the incised placenta extending downward to completely cover the internal cervical os. The routine technique of manual removal found 50% of the placenta firmly attached to the anterior cervix in the area of the previous caesarean section scar. No cleavage plane was identified. Transfusion of the first unit of blood had been started prior to this time and two ampules of oxytocin (Pitocin) were now added to the intravenous infusion. The placenta was removed piecemeal, leaving a shaggy bleeding area of stalactite-like placental fragments on the surface of the cervix. This area was observed for an eternity, perhaps four minutes, while the massive bleeding seemed to slow. With the patient in near shock and blood running at two sites, it was elected to close the vertical incision, hoping for hemostasis with the wide lateral bites in the cervical portion of the wound rather than to attack the formidable-appearing bladder flap. The abdomen was closed in fifteen minutes during which the patient's vital signs remained stable just above shock levels. When the drapes were removed a large pool of blood between the patient's legs on the table indicated marked continued bleeding.

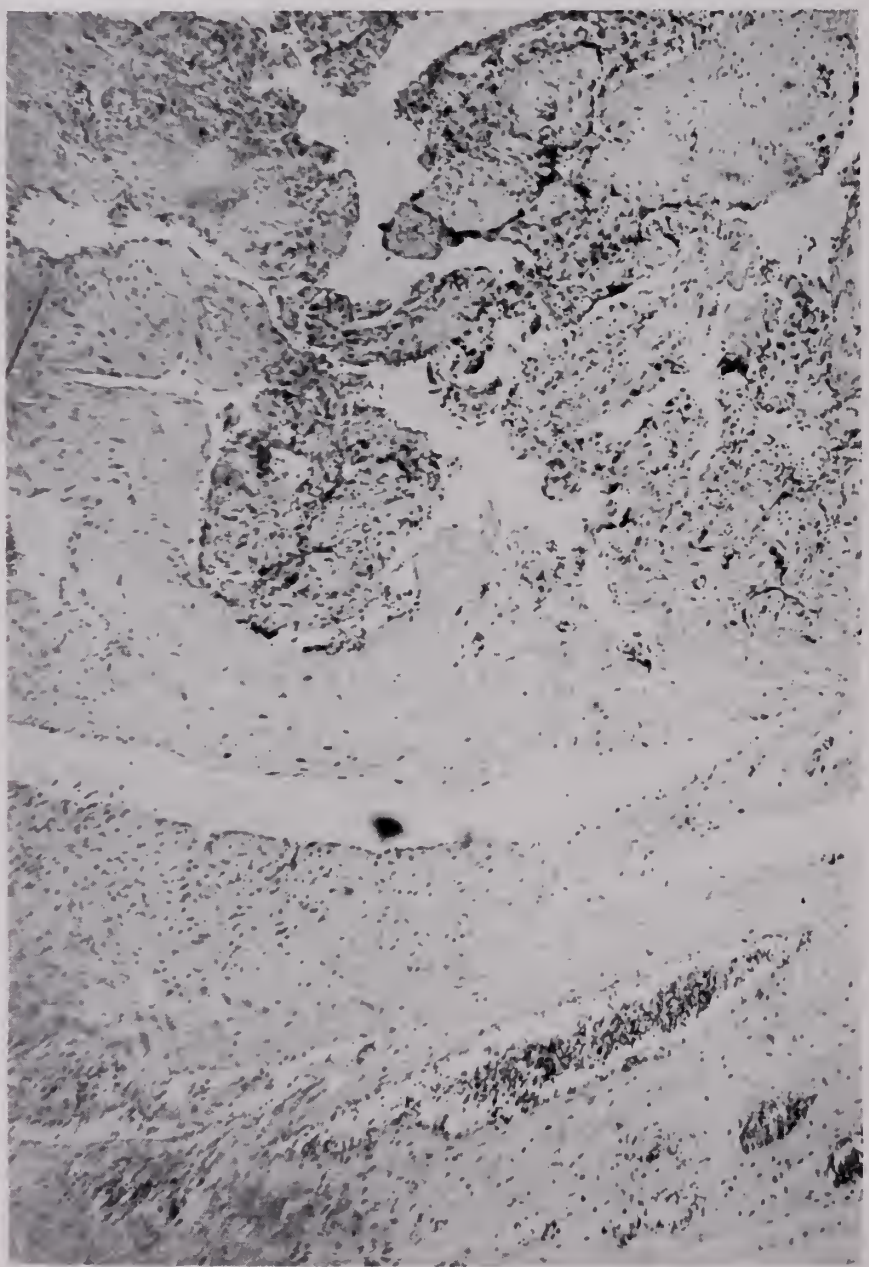
The Hysterectomy

The abdomen was re-prepped, re-entered, and a total hysterectomy carried out with dispatch. It was necessary

to insert two fingers through the slightly dilated cervix into the vagina to identify the junction of the anterior bladder due to distortion of the normal anatomy by the tremendous vascularity. The under surface of the bladder required numerous individual ties and ultimately an oxycel pack to control oozing. At this point all cut peritoneal surfaces were bleeding. A fibrinogen test was not done because the blood accumulating in the cul-de-sac was clotting normally. The vagina was closed without drainage. When the patient left the operating suite after eleven units of blood, her blood pressure was 90/60 and pulse 100.

Six additional units of blood were given in the postoperative period which otherwise was uneventful. Continued intra-abdominal oozing was suspected but not proved. Central venous pressure observations were discontinued on the third postoperative day. A total serum bilirubin on the second post-partum day was 1.05 mg %—the only laboratory abnormality in a galaxy of studies. On the seventh postoperative day the hemoglobin was 12.4 grams %. The patient was discharged one day before her daughter.

Microscopic sections confirmed placenta accreta (Figure). Villi were demonstrated within an estimated two mm of the serosal surface in the area of the previous caesarean section scar. This finding justifies a diagnosis of previa increta.



Figure—Photomicrograph taken through the entire cervical scarred area demonstrating a placenta halfway through the scar.

Discussion

The literature on this subject is easy to review because the condition is so rare and because recent articles are well done. In our review of the literature it became obvious that treatment of this condition by subtotal hysterectomy is foolhardy because vigorously bleeding areas are left behind. Those who did this partial procedure may have been frightened from the total operation by the same gigantic bladder flap vessels that concerned us, but succeeded with subtotal hysterectomy because collateral circulation to the cervix takes time to develop. It seems after our experience that a total operation is unquestionably the procedure of choice. In the account of the cases reported in the literature there seems to be a reluctance on the part of some authors to indicate accurately the amount of replacement blood transfused in the management of their respective cases. One author stated: "The patient was transfused back to normal levels." The least number of transfusions reported was three in a case in which no attempt was made to remove the placenta, and the most was 34—given in an heroic attempt to preserve the uterus of a woman who had lost her first baby.

In this case, the decision to close the abdomen and hope for hemostasis resulted in a loss of about 2000 cc of blood, and a closer brush with a maternal loss than we realized at the time. Such attempts are usually futile and not warranted unless Friesen's criteria for more conservative management are met: (1) Great motivation for preservation of the uterus (first pregnancy); (2) Recognition of the accreta before massive bleeding has occurred, and (3) Performance of the operation in a large medical center. In the case reported, the first two criteria were not fulfilled, but we would like to think the third was. In any case, the lesson to be learned from this case is: hesitation to perform a total hysterectomy in a case of placenta previa accreta may be a ticket to disaster.

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At a dinner for new faculty members at the university, I casually mentioned to the man in the next chair that "the facts had finally caught up with me," so that I quit smoking after getting up to over two packs a day and lost 75 pounds after achieving prodigious girth. The conversation moved promptly to other subjects, and I forgot all about it.

Nine months later, the same man walked into my office for a physical examination.

"Well, how do you like me?" he said. "Thirty pounds lighter, and no tobacco since September."

"Wonderful!" I said, trying to remember where I had seen him before.

"Don't you remember?" he went on. "That night at dinner—I figured that if you were convinced enough to *do* what you recommend, that was enough for me. And here I am!"*

*John E. Eichenlaub: The Minnesota Doctor's Home Treasury of Unusual Stress Easers, 1964.

A man always has two reasons for doing anything—good reasons and the real reason.—J. P. Morgan

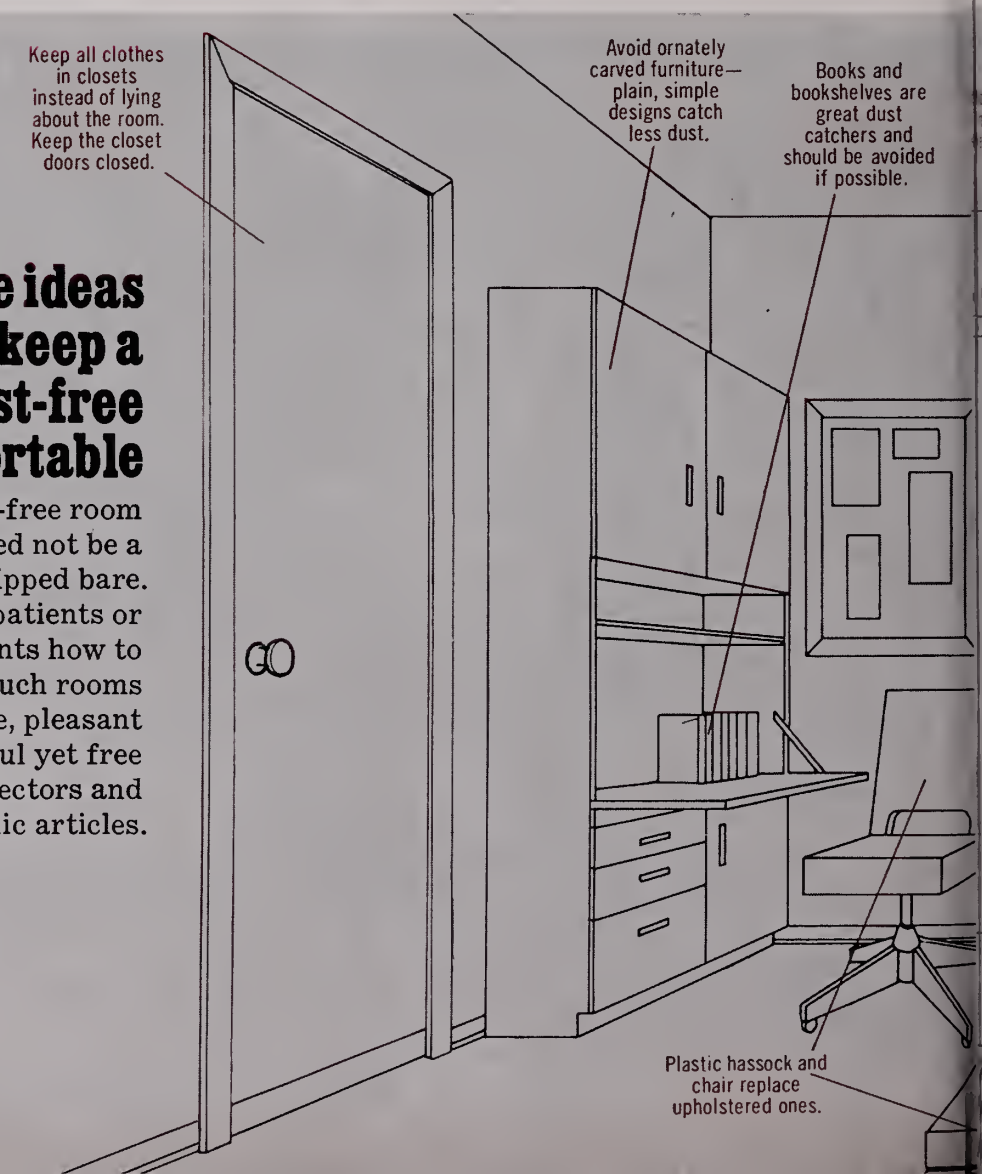
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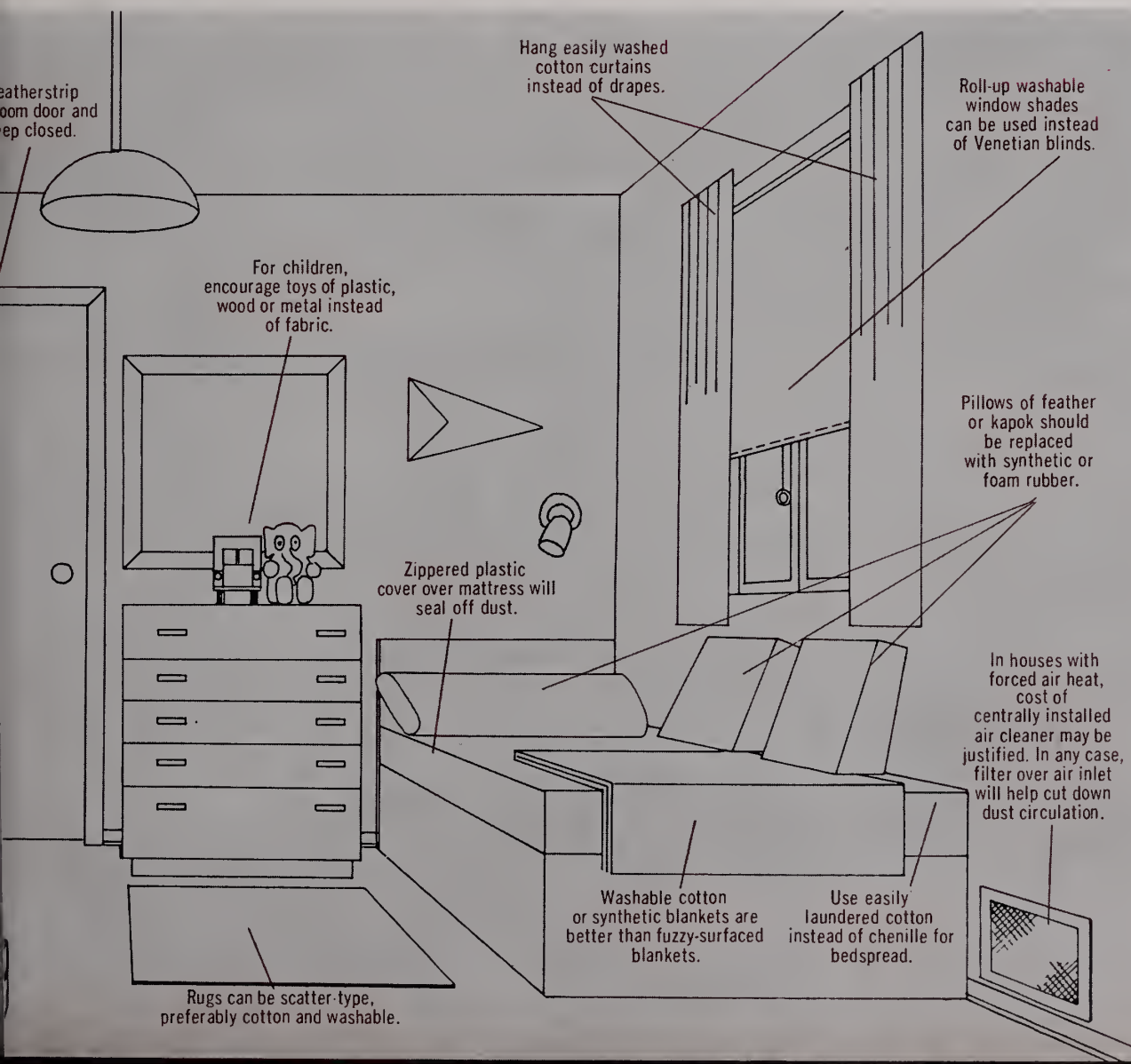
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Continued to page 556.



Fracture Conference

Multiple Fractures in One Upper Extremity*

Dr. John C. Ivins:

In your own practices and in ours, we see much trauma and many traumatic problems that are not absolutely fresh. Although they may not present the same difficulties as fresh fractures do, they are challenging. In order to get the proper perspective, I would like to review some of the objectives of fracture treatment. We have to keep in mind our objectives—whether or not the fractures are fresh.

Treatment at the Scene of Accident

Good on-site care of the injured is important so that any fractures produced by the accident itself will not be worsened by improper handling of the recipient. We want to *minimize fracture trauma* at the fracture site; we also want to minimize secondary trauma during our treatment of the fractures.

Restoration of Form

Although this is not always possible the restoration of normal form is certainly one of the most desirable of all objectives.

Uninterrupted Immobilization

Continuous and uninterrupted immobilization until healing occurs is not generally appreciated by those who do not work with fracture problems every day. There is an easy pitfall that you must be aware of: You look at the orthopedic textbooks and find that some of them state—and you uncritically accept—that such and such a fracture heals in eight weeks. So you apply the cast today, and in eight weeks remove it because the book says the fracture is going to be healed by that time. Of course, we know this is not exactly true.

*Fracture Conference, June 3, 1968.

Restoration of Function

We like to *restore function as early as possible*, compatible with healing. This does not mean that attempts to restore function necessarily need to be delayed until the fracture is completely healed, because there are mechanisms, of course, for starting function long before fracture healing is complete. This has to do most particularly with the small joints of the hand and those other joints that are not involved directly with the problem of healing of the fracture itself.

Maintain Patient Morale

We must consider that fracture problems may be long drawn out, may entail a lengthy convalescence, and may involve considerable economic loss. Thus, one of our great responsibilities is to *maintain morale for the patient* throughout the period of treatment.

Methods of Treatment

Closed Reduction

This assumes that the fracture itself is a closed one. In these cases, either a simple closed reduction or no reduction is done. The best example of a fracture requiring no reduction is a fracture of the proximal end of the humerus of an elderly patient. Closed reduction would be done in incomplete or minimally displaced fractures in the younger age groups.

Continuous Traction

Continuous traction is used in fractures of the long bones; for instance, fracture of the shaft of the femur of a young patient is an example of the use of continuous traction, although this method is not without its pitfalls and difficulties.

External Skeletal Fixation

This was used more frequently some years ago. It involves the use of apparatus such as the Stader apparatus and the Roger-Anderson apparatus. A good illustration of this method is the incorporation of pins in plaster-of-paris.

No Treatment

The next method is *no immobilization and no reduction*. Here again, impacted fracture of the proximal end of the humerus of an elderly patient is a good example.

Open Reduction

The last method is *open reduction and internal fixation.*

We shall discuss all of these a little more during the course of this conference.

Dr. Vu V. Nguyen:

The first case is that of a 42-year-old man who, while working in a ready-mix concrete plant, slipped and caught his right arm in the belt of the tightener wheel, suffering fractures of the right humerus and right forearm. He was transported to a local hospital where he was operated on the same day. A Rush nail was inserted into the humerus, and the right upper extremity was placed in a spica cast. He remained in this hospital about 10 days, dur-



Fig. 1—(A) Patient when first seen at our clinic, January 1968. (B) and (C) Right humerus, January 9, 1968, five months after injury. Fracture at junction of middle and lower thirds, with a Rush nail in place; fracture line still visible. (D) and (E) Right forearm, January 9, 1968, showing fracture of midshaft of radius and ulna, with slight angulation deformity. Absence of callus.

ing which time his right thumb became numb as a result of a radial nerve injury. After his arm had been in the spica cast for about nine weeks, a long-arm cast was applied and removed four months after the injury. At that time he had pain in the arm and forearm and could not extend the fingers of his right hand. There was also numbness along the extensor surface of the right forearm as well as on the dorsum of the thumb. He was first seen at our institution on January 9, 1968, nearly five months after the injury (Figure 1). We do not have the original *x*-rays, but we do have some taken when the patient first came here.

Dr. Ivins:

The injury was confined to the right arm and consisted of a closed fracture of the midshaft of the right humerus and of both bones of the forearm on the same side.

Dr. Nguyen:

When the patient came here, he had an un-united fracture of the right humerus at the junction of the middle and the lower third (Figures 1—B and C). The humerus had a Rush nail in place. He also had an un-united fracture at the midshaft of the right radius and ulna (Figures 1—D and E), and these bones were in a cast. The shoulder was stiff because of immobilization, and he could move his elbow only slightly. There was contracture of the wrist with the hand in palmar flexion and ulnar deviation. All the finger joints were stiff, with no active extension of the fingers. A sensory defect and complete denervation in muscles innervated by the radial nerve were noted on electromyography.

Dr. Ivins:

Because the hand is at the end of the arm, the problem became a hand problem. Dr. Bryan, will you please discuss the treatment of this?

Dr. Richard S. Bryan:

If the surgeon had operated on the forearm instead of the humerus, it would have been better. Insertion of a Rush nail is not a good method of treatment for this type of injury.

Dr. Ivins:

Would you discuss the initial treatment that you would recommend at this stage for what we now see: un-united fractures of both bones of the forearm, un-united fracture of the shaft of the humerus, and complete radial nerve palsy.

Dr. Bryan:

When both bones of the forearm are fractured in this locality, the treatment of choice is open reduction and plating, because there is no doubt that the end results are far better with such an approach than with any other method. I would do open reduction of the radius and ulna in this situation and fix them with compression plates.

Dr. Ivins:

Would you add a bone graft at the time?

Dr. Bryan:

No. I do not think it would be necessary. The next question then involves the humerus—whether or not it needs fixation. A radial palsy already exists, and it seems to me that the radial nerve should be explored and the humerus fixed at the same time. The radial nerve injury is much easier to repair, even if function does not return, in the sense that you can do tendon transplants that work to overcome the deficit of a permanent radial palsy. But, initially, if the nerve can be exposed and gotten out of the way, it probably is not torn, or is either caught in the fracture site or contused.

Dr. Ivins:

What was the interval of time between the injury and the patient's arrival at our clinic?

Dr. Nguyen:

Five months.

Dr. Ivins:

What is the chance of the radial nerve recovery after five months?

Dr. Bryan:

In one case that I recall, I took a screw out of the middle of one nerve at one year and sutured it together and got complete recovery.

Dr. Einar W. Johnson, Jr.:

In all of the comments so far, we have been discussing initial care of the fracture.

Dr. Ivins:

We seem to concur that open reduction with plating of both radius and ulna and open reduction of the fracture site of the humerus with inspection of the radial nerve would have been a better choice of initial treatment.

Dr. Johnson:

Do we know that the patient initially had a radial nerve lesion or was it a postoperative lesion?

Dr. Nguyen:

Postoperative. He was operated on the very day of his injury.

Dr. Johnson:

We do not really know then whether this was an immediate radial nerve lesion at the time or whether the lesion was found two or three days after his treatment.

Dr. Ivins:

We do not know. Let us have a brief description of the treatment rendered so far.

Dr. Nguyen:

Three days after the patient came to our clinic, his humerus was operated on. The Rush nail was removed, the fracture site was exposed, and the radial nerve was found to be divided. After resection of the neuroma, the humerus was shortened 4 cm in order to unite the nerve ends and the humeral fracture was fixed by a compression plate (Figure 2—A). A Bunnell dressing

was applied to the hand, and the arm was secured to the body by a Velpeau dressing. One week later, the patient's right forearm was operated on. The ulna was fixed with a Rush nail, the radius was held with a compression plate (Figure 2—B), and a Velpeau dressing was applied. Ten days later, a long-arm cast was applied.



Fig. 2—(A) Right humerus after surgery, January 16, 1968. Humerus has been shortened and fixed with a compression plate. Bone graft on fracture is clearly visible. (B) Right forearm after surgery, January 30, 1968. Ulna has been fixed with a Rush nail, and radius has been fixed with a compression plate.

Dr. Ivins:

What did the latest films indicate?

Dr. Nguyen:

The latest films were made on May 2, nearly four months after surgery at our clinic (Figure 3).

Dr. Ivins:

I think we can say this fracture is well stabilized. The humerus has healed and, as Dr. Nguyen pointed out, was shortened 4 cm in order to do a radial nerve anastomosis. That surgery was about five months ago.

Dr. Paul R. Lipscomb:

The patient still has a complete radial palsy because there is no function of the triceps, the wrist extensors, the brachioradialis, and the long extensors

of the digits. He still has hypesthesia in the thumb web. It is important to note that if I support his metacarpophalangeal joints, he can extend his interphalangeal joints, using the intrinsic muscles. Do not let this fool you. Likewise, if I support his thumb, he can extend the distal phalanx, using the adductor which inserts from the medial side and also the abductor brevis which inserts from the radial side. It has been 10 months since his injury and five months since the anastomosis.



Fig. 3—(A) and (B) Right humerus, May 2, 1968, four months after internal fixation. (C) Right forearm, May 2, 1968, three months after internal fixation.

Dr. Ivins:

Dr. Lipscomb, will you now give us your recommendations about treatment of the radial nerve deficit, and can you show us the range of shoulder motion? This is essentially all scapular motion on the chest wall. As you pointed out, there is no function of the triceps, and there is limited function in the elbow.

Dr. Lipscomb:

I would suspect that if the patient was going to improve, he would begin to show triceps function, also function in the brachioradialis and the wrist extensors. If these muscles are not functioning by this time, I think I would proceed with the definitive tendon transfers, because the chances of functional recovery are so much less in a man of his age than they are in some-

one in his twenties. Moberg, who has done a lot of work on nerve recovery in this type of injury, points out that in patients more than 35 years of age, the chances of nerve recovery decrease tremendously. Thus, with an injury of this type, with no evidence of recovery, I think we could go ahead with the definitive tendon transfers.

Dr. Ivins:

The last electromyogram, done on May 2, indicated complete denervation of the muscle supplied by the radial nerve, except for some fibrillation potentials in the triceps. I believe that this case of multiple fractures in one upper extremity illustrates some of the concepts of treatment and leaves us with these important points:

1. Fractures of both bones of the forearm need internal fixation, which should be done as a primary form of treatment.
2. The presence of the radial nerve injury complicating the humeral fracture indicates need for exploration of the nerve and fixation of the humerus.
3. After all fractures are immobilized properly, the adjacent joints can be kept active and freely movable.
4. Several months after fracture, if it seems fairly certain that function of the radial nerve will not return, recourse to the tendon transfer procedure to overcome this loss of function is indicated.

John C. Ivins, M.D.*
Vu V. Nguyen, M.D.*
Einer W. Johnson, Jr., M.D.*

*From the Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

Contributors to Science

Like Magendie, Bernard used live animals in his demonstrations and based his courses on his own research. His reputation as a teacher began to grow. In 1853 one of his students wrote, in a French medical journal, "Everyone knows with what eagerness pupils flock to this young and eminent professor."

Many of the pupils were Americans. After graduating from American medical schools, young doctors went to Europe for advanced study if they could afford to, and in the 1850's they went to France.

Francis Donaldson, a doctor from Maryland, wrote: "It was curious to see walking about the amphitheatre of the College de France dogs and rabbits, unconscious contributors to science, with five or six orifices in their bodies from which, at a moment's warning there could be produced any secretion of the body, including that of the several salivary glands, the stomach, the liver, and the pancreas."*

*Jerome Tarshis: Claude Bernard, Father of Experimental Medicine, 1968.

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1. Kannel, W.B., *et al.*: *Circulation* 35:734, 1967.
2. Thomas, H.E., Jr., *et al.*: *Med. Times* 95:1099, 1967.
3. Albrink, M.J., in: Beeson, P.B. & McDermott, W. (eds.): *Cecil-Loeb Textbook of Medicine*, ed. 12, Phila.: W.B. Saunders Co., 1967.

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Classified Advertising

Continued from page 542

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Review

Polycythemia

Differential Diagnosis and Treatment

HAROLD SEIM, M.D.*
Sioux Falls, South Dakota

POLYCYTHEMIA, DEFINED as an excessive number of red corpuscles in the blood, is a relatively common entity as shown by a survey of 6,000 general hospital admissions, of which 62 were noted to have hematocrit values greater than 54%.[1] This entity can be divided into three general types, described in the following paragraphs.

Relative Erythrocytosis

Relative erythrocytosis usually occurs as a result of loss of fluid and electrolytes from the intravascular spaces, leading to hemoconcentration. Some conditions in which this occurs are burns, shock, decreased fluid intake, acidosis and loss of fluid as in diarrhea and profuse sweating. Correction of this type of erythrocytosis will follow correction of the cause for fluid loss.

Secondary Erythrocytosis

Secondary or absolute erythrocytosis, in which there is an actual increase in red cell mass, is usually secondary to one of several causes which make up the bulk of the considerations in the differential diagnosis of polycythemia.

Arterial Oxygen Saturation

Low oxygen saturation may be seen in cyanotic congenital heart disease such as persistent truncus arteriosus, tetralogy of Fallot, transposition of the great vessels and right-to-left shunts as in patent foramen ovale, interventricular and interatrial septal defects. Pulmonary stenosis associated with a right to left shunt is the commonest low oxygen saturation defect causing polycythemia.[2]

Defective pulmonary oxygenation is a second reason for low oxygen saturation and is seen in emphysema or fibrosis of the lungs, where there is an infiltration, replacement or compression of the lung tissue by substances other than lung tissue. Ayerza's syndrome is an example. It is a slowly-developing asthma, bronchitis, dyspnea and cyanosis associated with polycythemia, in which those afflicted are known as cardiacos negros (black cardiacs). There is splenomegaly, clubbing, passive congestion of the liver and chronic heart failure, often due to dilatation and hypertrophy of the right atrium and right ventricle.[3]

"Alveolar-capillary block syndrome," that is, disorders associated with diffusion impairment such as sarcoidosis, tuberculosis, histoplasmosis, asbestosis, silicosis, alveolar cell carcinoma and cavernous hemangiomata of the lung also result in low arterial oxygen saturation. Pulmonary arteriovenous fistulae are associated with polycythemia, cyanosis and clubbing of the fingers, and mimic the congenital forms of heart disease, but are without cardiac findings; frequently a bruit is heard over the involved area in the lung. These A-V fistulae shunt significant quantities of blood through the lungs without allowing sufficient contact with the oxygen in the alveoli, resulting in deficient oxygenation of the blood.

Diseased pulmonary arteries as in pulmonary hypertension with pulmonary arterial and arteriolar sclerosis may be accompanied by asthma, bronchitis, dyspnea, cyanosis and polycythemia.[2]

Obesity with Right Ventricular Failure

Polycythemia is seen in obesity with right ventricular failure as in the Pickwickian syn-

*Written as a Senior Medical Student, University of Minnesota Medical School. Now interning at the Sioux Valley Hospital, Sioux Falls, South Dakota.

drome. This syndrome is characterized by somnolence, marked obesity, cyanosis, periodic respiration, secondary polycythemia and right ventricular failure. The polycythemia is secondary to alveolar hypoventilation caused by an increased work load due to excessive fat deposition. Kyphoscoliosis can also cause a polycythemia as a result of an increased pulmonary work load imposed by the thoracic deformity.

Environmental

High altitudes and low barometric pressure are two environmental conditions that lead to a secondary polycythemia. Here, the decreased oxygen content or lowered barometric pressure of the inspired air results in a compensatory increase in red cells to carry adequate oxygen to the body tissues.

Chemical and Physical Agents

Exposure to chemical and physical agents can lead to a true erythrocytosis by producing abnormal hemoglobins which do not transport oxygen well, such as methemoglobin and sulfhemoglobin. Acetanilid, phenacetin, aniline dyes, nitrates and nitrites, sulfas, prontosil and phosphorus are examples of such agents. Cobalt, on the other hand, is thought to act by stimulating erythropoietin production.

Miscellaneous

Finally, a miscellaneous, non-hypoxic group of secondary polycythemias is recognized.

Renal disorders have been shown to produce erythrocytosis. Hypernephroma is most common in this group; other less common disorders are hydronephrosis, polycystic kidneys, renal carcinoma, adenoma and sarcoma. Plasma erythropoietin levels have been elevated in most cases of renal tumors and the polycythemia has disappeared after the associated tumor has been removed.[2] After renal transplantation Marlin and Goodwin have observed a progressive rise in hematocrit in all patients following successful renal transplant.[4] A postulated mechanism for this phenomenon is that the transplanted kidney is stimulated to produce erythropoetin because of ischemia or other damage.[5]

Infratentorial tumors, notably hemangioblastomas of the cerebellum and, more rarely, other tumors such as hepatomas, hepatic carcinoma, uterine fibromas and myomas, and neoplasms of the adrenal, ovary and liver are known to produce erythrocytosis.[5]

Moderate erythrocytosis may be found in *Cushing's syndrome,* and can also be produced by administering large doses of corticosteroids.[2]

Stress erythrocytosis (benign polycythemia or Gaisbock's syndrome) is a term applied to the polycythemia seen in very active, hard-driving persons in a state of anxiety, who have the characteristic plethoric appearance, hypertension and vascular disease. The red cell mass is normal in these persons and the plasma volume is below normal, but no primary cause has been recognized; whether this is a true syndrome or just a group of individuals outside the accepted norm is not clear. These patients appear to receive little improvement from phlebotomy, as the hematocrit still remains high and a subjective feeling of dizziness persists. As the erythropoietic tissue is normal, P^{32} is contraindicated.

A rare type of polycythemia may be found in individuals with abnormal hemoglobin characterized by increased oxygen affinity.

Polycythemia Vera

The third major type of polycythemia is polycythemia vera or erythremia, differing from the other polycythemias in that it is a disease of unknown etiology classified with the myeloproliferative disorders in which there is usually a pancytosis of the bone marrow and an increase in the peripheral red cells and often of white cells and platelets. Splenomegaly, plethora, headache, dizziness, tinnitus, dyspnea, lassitude, pruritus, hemorrhages, thromboses and neurasthenias are commonly associated findings. The spleen is enlarged chiefly due to hyperplasia of the pulp and distention with blood. Infarcts of the spleen are common and there are often extramedullary foci of blood formation in the spleen and liver. Wasserman reported 61 cases of myelofibrosis with myeloid metaplasia, in which 58% had a suggestive history of polycythemia vera.[6]

Characteristics

Polycythemia vera is characterized by an in-

creased red blood count, elevated hematocrit, blood volume, red cell mass and a normal or increased plasma volume.

There is usually thrombocytosis and leukocytosis; there may also be nucleated red cells in the peripheral blood and increased leukocyte alkaline phosphatase, serum B_{12} and uvitic acid.

The bone marrow in erythremia is usually solidly hypercellular with hyperplasia of all marrow elements. The percentage of nucleated red cells is generally elevated, and megakaryocytes may be markedly increased.

Clotting Mechanism

There is a paradox in clotting mechanisms in polycythemia vera. Due to the decrease in the circulatory minute volume and decreased blood flow velocity, there may be vascular stasis which, together with the thrombocytosis, causes a high incidence of thrombosis. Hemorrhage may also be a complication in polycythemia vera and is thought to be due to alterations in platelet function and/or adhesiveness and to increased friability of the clot. Hemorrhage may also be due in part to the distention of the capillaries and veins to accommodate the increased blood volume.

Blood Volume

Determinations of the blood volume, red cell mass and plasma volume are essential in the evaluation of polycythemia. The hematocrit value gives the first clue to an elevated red cell mass, although Lawrence[7] has shown that the hematocrit may be high with a normal red cell volume and that patients with increased hematocrit do not necessarily have an increased red cell volume.

Radioiodinated serum albumin (RISA) is used to calculate the plasma volume, and Cr^{51} or P^{32} tagged red cells are used to measure total red cell mass. Plasma and red cells, after they are washed free of plasma, can be measured separately or by using a gamma-ray spectrometer which analyzes pulse height. Both values may be measured simultaneously.

Lillehei et al.[8] have noted that, although arterial oxygen saturation is usually normal in patients with polycythemia vera, it may sometimes be reduced. For unexplained reasons, alveolar-arterial gradients were found to be high in untreated polycythemia vera despite relatively normal pulmonary function. These indicate venous-arterial admixture presumably due to opening of arteriovenous communications as a consequence of the high blood volume. Invariably with reduction of the elevated hematocrit, the elevated arterial-alveolar gradient would decrease.[9]

Murray measured arterial oxygen saturation of normals and of patients with various disorders including chronic lung disease with hypoxia, neoplasia, congestive heart failure and polycythemia vera. Average saturations in all other disorders were higher than in the severely hypoxic patient, but the overlap is great enough so that the determination of arterial pO_2 may not be adequate to make the differential diagnosis. It is possible for the oxygen saturation in all of these disorders to be 90%.

A more recent and very interesting technique has been developed by Brodsky et al.[10] for differentiating polycythemia vera from other polycythemias. He evaluated 22 patients with polycythemia vera, six with benign polycythemia and six with secondary polycythemia, by using ferrokinetic studies and measurement of bone marrow iron stores. In polycythemia vera, there was poor correlation between hemoglobin, packed cell volume and total red cell mass. However, there was a rapid Fe^{59} T½ (less than 30 minutes) in 85% of the patients, and 21 of 22 patients had absent marrow iron stores. In both secondary and relative polycythemia the Fe^{59} T½ was normal and stainable iron was present in the marrow. The rapid Fe^{59} T½ in polycythemia vera is considered to be due to iron deficiency and is used as an index of the increased erythropoiesis.

Ellis[11] reported prolongation of plasma iron disappearance time in patients with untreated polycythemia vera when marrow stores were repleted; however, the change in plasma iron disappearance was minimal when iron administration was insufficient to replete marrow stores.

Summary

Relative polycythemia is characterized by an elevated hematocrit but has normal or decreased blood volume, red cell mass and plasma volume. Secondary polycythemia of the hypoxic type or that secondary to renal disease and

some tumors is characterized by an elevated hematocrit, blood volume, red cell mass and a normal or increased plasma volume. Arterial oxygen saturation may be normal but is usually decreased in the hypoxic type. Polycythemia vera has these same findings but usually has normal oxygen saturation and tension. Low arterial pO_2 is the significant factor in differentiating primary and hypoxic secondary polycythemia, although partial pressure of oxygen does not always adequately provide this differentiation.

Treatment

Treatment of relative erythrocytosis consists of fluid administration, as well as correction of the underlying cause for the fluid loss, such as rehydration of the burn patient or the patient in shock, correcting acidosis or the cause of the diarrhea or excess sweating.

Correction of Underlying Condition

Treatment of true secondary erythrocytosis also rests on correction of the underlying condition causing the increased red cell mass. Repair of a congenital heart defect; loss of weight in the Pickwickian syndrome; a move from a high altitude closer to sea level; removal of a renal, cerebellar or uterine tumor will often be the therapy needed in such cases. In certain others, along with correcting the underlying causes for the polycythemia, the cautious use of phlebotomy to decrease the hematocrit may be helpful in prevention of thromboses or in reducing circulatory overloading. In other situations, such as transposition of the great vessels, emphysema or pulmonary fibrosis, sarcoidosis or asbestosis, pulmonary arteriolar sclerosis and kyphoscoliosis, the cause is essentially uncorrectable and the increased red cell mass is needed to transport sufficient oxygen for the body tissue needs. In these cases the red cell production may "overshoot" and occasional phlebotomy may be advisable.

Decrease Hypervolemia

In the treatment of polycythemia vera the objective is to decrease erythrocytic hypervolemia, but there is no consensus of opinion as to the best treatment. Stroebel and Hanlon[12] have outlined their recommendations for therapy as follows: Initial treatment is accomplished by repeated phlebotomies of 500 cc. per day in healthy persons or of 250 cc. per day in elderly patients or in those with cardiovascular disease. It is important to know the original erythrocyte volume and hematocrit; the progress of therapy can then be monitored by monthly hemoglobin and hematocrit values. With repeated blood loss, iron deficiency may become a problem; if the serum iron level drops below normal, iron therapy may be necessary.

Myelosuppressive Therapy

Six indications for use of myelosuppressive therapy are as follows:[12]

1. a. Rapid relapse of erythrocytic hypervolemia after initial phlebotomy.
   b. Necessity for phlebotomies more than every two months to keep hematocrit below 55%.
2. a. Platelets over 500,000 per mm^3.
   b. Defective platelet quality.
   c. History of thrombosis or hemorrhage.
3. a. Marked hyperuricemia.
   b. Urinary calculi in patients who are unable to tolerate allopurinol.
4. Failure of marked splenomegaly to remit.
5. Failure of repeated phlebotomies to give relief of such symptoms as headache, malaise, myalgia, pruritus, gastrointestinal symptoms, weight loss, peptic ulcer.
6. Non-feasibility of phlebotomy due to poor veins, distance from hospital, etc.

The two main types of myelosuppressive therapy employ radiophosphorus or alkylating agents. Stroebel and Hanlon[12] recommend administration of radioactive phosphorus and prefer the intravenous route because oral absorption is unreliable. Prediction of an adequate dose of P^{32} is inaccurate; a dose of 3 mc. is given as the usual starting dose, but if there is marked leukocytosis, thrombocytosis and splenomegaly, then an initial dose of 5 mc. is given. The effect of radiation on platelets is evident by three weeks, but the full effect on red cells is not complete for three months; therefore patients are reexamined at three-month intervals. If there is no remission at this time, 5 mc. is administered and repeated in another three

months if indicated. The total dose of P^{32} should not exceed 15 mc. in the first year or 6 mc. per year subsequently. With this therapy, 75% have remissions for one year; slightly over a third of patients have remissions for three years.[12]

Comments

Cases have been reported in which polycythemia vera is transformed into acute leukemia, especially after treatment with P^{32} which has been thought to be responsible. Brodsky et al.[10] noted that the increased incidence of acute leukemia in polycythemia vera patients treated with P^{32} is dose dependent, increasing significantly in patients given more than 12 mc. Norcross[13] reported a leukemia incidence of 1.7% in polycythemia patients treated with doses under 15 mc., and 28% at a total dose of 40 mc. and over. Doses of P^{32} given to patients who died from leukemia ranged from 45 to 116 mc., with leukemia developing from eight to ten years after the initial dose of P^{32}. Yu and Krakoff[14] agreed that acute leukemia does develop in patients treated with P^{32}, but note that these patients also survive longer than others. Many observers feel that the transformation to acute leukemia is part of the natural course of the disease rather than a complication of P^{32} therapy.[9,14] Modan and Modan reported that 6% of non-irradiated and 18.5% of irradiated cases of polycythemia vera developed a myeloproliferative disorder.[15]

Alkylating agents are the second type of myelosuppressive therapy used to control the pancytosis of polycythemia vera. Myleran (Busulfan) in doses of 2-6 mg./day, has given good results, but thrombocytopenia, leukopenia, or both are evident before the red cell mass is affected. The erythrocyte hypervolemia can be decreased by concomitant phlebotomy in these cases. Jerde[6] reported on three independent studies totalling 35 patients, which showed good results in 29 and incomplete remission in six patients on busulfan therapy. Brodsky et al.[10] reported on treatment of 15 patients with busulfan, 14 of whom obtained remission after 112 to 312 mg. was given over 34 to 71 days. In one case, 1,080 mg. was given over a period of one year to obtain remission. These investigators feel that the total dose given is more critical than the dose rate, and recommend stopping when platelets reach 300,000/ cu. mm. Remission in this series was six to twelve months, with one patient in remission for two years.

Advantages of radiophosphorus treatment are that little supervision is needed, the method of administration is easy, especially with the oral form, and remissions are of long duration.

Disadvantages of chemotherapy are the need for frequent close observation of the patient and usually shorter remissions than with P^{32}.

The average survival time of untreated cases of polycythemia vera has been reported to be five years.[13] Prognosis with therapy has been encouraging, several series showing median survivals of about 13 years.[9,17] Norcross[13] reports a study by Stroebel in 1954 in which, with P^{32} therapy, a gain of 20 years in mean survival was obtained in patients whose death was due to hematological causes and a gain of ten years in survival in patients whose death was nonhematologically related.

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I pity the man overwhelmed with the weight of his own leisure.—Voltaire.

Historic Hospitals

Allgemeines Krankenhaus, Vienna



Vienna. Allgemeines Krankenhaus. Engraving 1793 by Joseph and Peter Schaffer. National Library of Medicine. Bethesda, Maryland.

Vienna began its rise to medical pre-eminence in 1745 with the arrival from Leyden of Gerhard Van Swieten and his eventual founding of the Old Vienna School.

For another forty years, however, the conditions in Vienna's hospitals remained as deplorable as anywhere else in the eighteenth century. Patients were scattered about the city in a bewildering array of small, poorly managed hospitals where food and sanitation were bad, nursing care inadequate, and mortality rates high.

In 1780, the reforming Emperor Josef II succeeded to the throne and promptly applied himself to the social and health problems of the Empire. He decided that the remedy for Vienna's poor hospital conditions was to replace most of the small substandard institutions with one large general hospital under highly centralized management. He determined to convert the Gross Armenhaus, a spacious almshouse and apartment building for students, into the new Allgemeines Krankenhaus. His personal physician, Josef von Quarin, drew up the plan for the remodeling, and became the hospital's first director.

The hospital, opened in 1784, was designed to accommodate about two thousand patients and had, for those times, a generous budget. An enlightened policy governed the admission of patients; none could be refused admission, and payment was determined according to the family's means. Privacy and dignity were accorded the patients in a manner unusual for the times. Physical conditions were good and care of the patients much improved.

While the hospital represented a significant social advance for the people of Vienna, its great world fame came about through the opportunity for clinical research and pathologic study which was provided by the concentration of so many patients into one well-managed institution. Before the turn of the century, thousands of autopsies had been done and a museum of pathologic specimens instituted. In the next century, Rokintansky Skoda, Hebra, Semmelweis, Billroth, and many other physicians of the Allgemeines Krankenhaus made Vienna the medical center of the world.

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Grand Rounds

Polymyalgia Rheumatica*

A Clinical Form of Giant Cell Arteritis

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POLYMYALGIA RHEUMATICA is not a rare disease according to recent studies;[2,6] however, the entity often goes undiagnosed because of unfamiliarity with the symptom complex by practicing physicians. Because of certain morbid and even lethal complications of giant cell arteritis which are often preventable by treatment, this disease should be familiar to all physicians.

Polymyalgia rheumatica is a clinical form of giant cell arteritis. Another more commonly recognized form is temporal arteritis; indeed both forms often occur in the same patient. Still another probable clinical form includes Takayasu's disease or the aortic arch syndrome.

Age Incidence

Polymyalgia rheumatica afflicts persons in the seventh, eighth, and ninth decades. Women greatly outnumber men, usually reported as seven or eight to one. The disease most often begins abruptly, so that patients can recall the hour or day when symptoms began. Initially pain, located in the pectoral and pelvic girdle muscles or neck, occurs without weakness or stiffness. Pain is also common in the low back, calf muscles, biceps and triceps. The pain is not constantly present but is marked upon motion, especially in the morning upon arising. Associated with the pain is headache, malaise, fever, anorexia, weight loss, lassitude and depression.

Physical Findings

Upon examination the muscle groups involved are tender, but this finding is not as pronounced as upon motion. Weakness is secondary to pain and is not notable. Atrophy and wasting of the muscles are not present. The joints are usually unremarkable for the patients' advanced age, although rarely has an asymptomatic effusion been found. Palpation of the temporal arteries

*Presented as a Medical Grand Rounds at Hennepin County General Hospital, September 16, 1969.

may reveal induration, tenderness and absent pulse, typical findings in temporal arteritis. Periorbital and facial edema may also be present. The temperature is usually elevated and may go as high as 103 degrees. Nodules in the skin and subcutaneous tissues are absent.

Laboratory Evaluation

Laboratory evaluation shows a remarkably elevated sedimentation rate, a hallmark of the disease; most values are above 100 mm. by the Westergren method. A mild anemia of either the normochromic or hypochromic* type is usually present. Bone marrow aspirates are unremarkable for cellularity and iron stain. Serum alpha globulins and fibrinogen are almost always elevated. Occasionally beta and gamma globulins are also elevated. Serum albumin is usually low. An electromyleogram, serum transaminase and muscle biopsies are normal. Tests for rheumatoid factor and lupus erythematosus are negative. Joint survey shows x-ray changes compatible with age.

Differential Diagnosis

The differential diagnosis includes rheumatoid arthritis, polymyositis, multiple myeloma, occult malignancy, polyarteritis nodosa, systemic lupus erythematosus, fibrositis and peritendinitis.

Rheumatoid arthritis may be ruled out when objective joint findings are lacking. Also a positive rheumatoid arthritis factor would be expected 80 percent of the time. Polymyositis presents with muscle atrophy, high serum transaminase levels, evidence of myositis on muscle biopsy and electromyographic changes. Multiple myeloma is recognized by bone destruction on x-ray, myeloma cells in the bone marrow aspirate, and typical urine and serum protein abnormalities. Malignancy is ruled out by the passage of time and the remarkable response to steroids in polymyalgia rheumatica. Polyarteritis is distinguished by the presence of renal disease, eosinophilia, pulmonary disease, neuropathy and microscopic evidence of necrotizing vasculitis. Lupus erythematosus is usually found in much younger patients, manifests multi-system disease, and lupus erythematosus cells are usually found. Fibrositis and peritendinitis are recognized by their localized nature, lack of systemic symptoms and normal laboratory findings.[8]

Comments

In a retrospective study[6] the course of the untreated disease was noted. Symptoms increased to reach a peak within a few weeks or months and then subsided over a period of months or years—usually years. Upon treatment with steroids, however, the patient who may be so incapacitated as to be confined to a wheelchair or bed will become asymptomatic within 72 hours. One author states that if such relief is not forthcoming in the stated time interval the diagnosis of polymyalgia rheumatica is subject to grave doubt.[27]

Review of the literature finds a relative paucity of recordings and discussion of this disease. In the American literature no cases of giant cell arteritis presenting as polymyalgia rheumatica had been reported until 1963; the next report was in 1965.

Barber[5] of Britain suggested the name polymyalgia rheumatica in 1957, although other authors[1,4,10,14,18] had written of the disease under various names and as early as 1888.[7]

*See Test Your Word Score, page 523.

It is interesting to follow the development of the disease polymyalgia rheumatica as it became recognized in the literature as a clinical form of giant cell arteritis. Temporal arteritis had been known as a clinical form of giant cell arteritis prior to 1957 when Barber named polymyalgia rheumatica. Symptoms of polymyalgia rheumatica were noted to precede the onset of temporal arteritis, almost as if polymyalgia rheumatica were a prodrome in occasional patients.[23] In fact Porsman[23] in 1951 and Paulley[21] in 1956 suggested that temporal arteritis and polymyalgia rheumatica were probably the same disease. In 1960 Paulley and Hughes[20] deduced from a series of 76 cases of temporal arteritis that polymyalgia rheumatica was the same disease in a different guise. Within a few years temporal artery biopsies were performed in cases of polymyalgia rheumatica and reports of a significant number of positive biopsies came from Scandinavia. Alestig and Barr[1] in 1963 reported 10 cases of polymyalgia rheumatica, none of which showed symptoms or findings of temporal arteritis. Seven of nine biopsied were positive for temporal arteritis, however. Hamrin et al.[19] in 1964 biopsied 21 cases of polymyalgia rheumatica and found 12 positive for temporal arteritis. In 1965 they[12] extended their series to 48 biopsies and found 21 cases positive for temporal arteritis. At the same time Hamrin et al. reported hearing 100 different non-cardiac murmurs in 30 patients in their series, and angiography in five of these patients showed stenosis at the site of the murmur. In 1968 Hamrin et al.[13] reported the results of six autopsies from the previously reported series in which the non-cardiac murmurs had been heard. Four of the six showed giant cell arteritis in the aorta or its main branches and a fifth had had a positive temporal artery biopsy during life. From these series and others there is evidence that polymyalgia rheumatica and temporal arteritis are manifestations of the same disease, namely giant cell arteritis.

There is also accumulating evidence that giant cell arteritis affects many large and medium-sized arteries in the body and that clinical conditions such as Takayasu's disease (subclavian artery stenosis) may also represent other clinical manifestations of systemic giant cell arteritis.[2,12]

Depression has been frequently noted as a prominent symptom in more than one series of giant cell arteritis[15,20] and is attributed to the involvement of the intracranial and meningeal arteries. Renal and cardiac symptoms have been touched upon only lightly in the literature to date.

Microscopically the biopsied vessel, usually the superficial temporal artery, shows a typical picture when positive. Giant cell arteritis is characterized by giant cells of either the Langhan's or foreign body type in the medial layer. The medial layer in addition shows cellular infiltration of predominantly lymphocytes; but neutrophils, plasma cells, eosinophils, and macrophages may also be present. Necrosis and fragmentation of the internal elastic lamina completes the picture in the media. The intima shows an attempt at connective tissue repair and is often so thickened with loose connective tissue that the vessel lumen is severely compromised. The clinical correlation of this last microscopic finding may be the symptoms of giant cell arteritis in its various guises. "Skip areas" occur frequently, so that a negative biopsy does not rule out giant cell arteritis.

Temporal arteritis with involvement of the ophthalmic artery is well known to cause blindness. For this potential complication of polymyalgia rheumatica, if for no other, it is important to begin immediate treatment with steroids. In addition, steroids dramatically relieve the symptoms of polymyalgia rheu-

matica—within 72 hours. It is not known, however, whether the total duration of the disease is shortened with steroid treatment. Even if positive biopsy results are not forthcoming, the patients who present with symptoms typical of polymyalgia rheumatica should be treated with steroids if all other diseases have been ruled out. A typical treatment schedule would be 40-60 mg. prednisone daily in divided doses with tapering by 10 mg. every two days until a daily dose of 15 mg. is reached. The tapering would then proceed more slowly with a reduction every two weeks by 2.5 mg. Occasionally steroids may be necessary for many months or even years.

Case Report

The patient is a white woman 69 years of age. During the first week of February, 1969, she noted pain about both temporal mandibular joints after a "flu" syndrome. One month later she noted pelvic girdle and right shoulder pain upon motion, most marked in the morning upon arising. Concomitant with the pelvic and shoulder pain the patient experienced headaches and gold rings in the left field of vision. For the three months preceding hospitalization she had had marked lassitude and malaise. She was anorexic and had lost twenty pounds.

Physical examination was unremarkable with the exception of marked limitation of motion of the right shoulder thought to be secondary to pain. The joints were normal as were both temporal arteries. The temperature was 99.4° orally.

Laboratory examination showed a hemoglobin of 9.3 gm. %, a sedimentation rate of 121 mm/hour, and a normal SGOT and CPK. Bone x-rays showed diffuse osteoporosis and a localized Paget's disease of the left tibia. Rheumatoid arthritis and lupus erythematosus tests were negative. A left temporal artery biopsy showed giant cell arteritis.

After the temporal artery biopsy the patient was given 40 mg. of prednisone daily in divided doses. On the fourth day of steroid treatment her hemoglobin was 12 mg. %, the sedimentation rate was 16 mm/hour and her muscle pain had diminished significantly. She was discharged from the hospital the next day on 30 mg. of prednisone a day. Three weeks later the hemoglobin was 14 mg. % and the sedimentation rate, 10 mm/hour. Four weeks after discharge the range of motion in the right shoulder was full.

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It's the Law

Chiropractor Convicted of Murder in Cancer Patient's Death

A California court convicted a chiropractor of second degree murder in connection with the death of an eight-year-old girl, who was suffering from a melanoma of the left eye. The chiropractor had treated the child for 21 days by the administration of vitamins and diet supplements. He allegedly told the child's parents that the treatment would cure the cancer. He charged the parents an excessive $700 for treatments.

News Release, Los Angeles, California, Dec. 1, 1967.

Editor's Note: Prior decisions in this case were reported in The Citation 13: 9: 173, 11: 5: 87, and 6: 3: 24. The Citation 16: 7, January 15, 1968.

Experience

A country doctor once advised his son not to embark on medicine as a career and then, thinking out loud, explained himself by saying, "I guess I am so close to the forest that I can see the trees."

—Robert Fetridge.

Didactic

Pseudobulbar Palsy*

THE TERM "pseudobular palsy," a misnomer, is a paralysis of the medulla's function due to bilateral lesions within the corticobulbar tracts. Dysarthria,† dysphagia, a loss of facial expressiveness, sialorrhea and a loss of usual emotional control are the manifestations of this disorder.

Symptoms

Dysphagia

The dysphagia which develops may be severe, but it frequently moderates within days, permitting the patient to swallow once again but only with a studied slowness. Spontaneous swallows, which most normals can perform three times in rapid succession, is slowed, and often only one or two slow deliberate swallows are possible for these individuals. The dysarthria is usually quite obvious to the ear, the speech is akin to that which can be produced if the jaws are held open and the tongue held immobile.

Paretic Facies

The facial muscles of expression and mastication are paretic and result in an expressionless face with a sagging jaw. Power to close the mouth is usually present but impaired for long continued contraction. In the resting position the mouth remains open and, due to loss of automatic swallowing, saliva drools from the mouth.

Emotional Lability

Patients also manifest less than clearly understood emotional lability, most prominent immediately after the onset of severe pseudobulbar palsy and less evident with time. Spontaneous crying is the most frequent form, most often precipitated by subjects with an emotional charge. Some severe cases manifest the response constantly at first; even conversation totally devoid of personal emotional content may cause uncontrolled sobbing. The crying may last for several minutes and recur repeatedly, making communication almost impossible.

Much less common is spontaneous laughter which is more commonly seen in the insidious forms of pseudobulbar rather than the sudden variety. It also occurs in response to emotionally-charged conversation material but may be totally inappropriate. Topics which would be expected to produce sorrow may result in a very loud burst of laughter, often perplexing the examiner and distressing the patient.

This clinical syndrome of pseudobulbar palsy is familiar to all who treat patients with neurological disease. It may help to have a differential diagnosis

*Presented at Neurology Continuation Course on Neurological Emergencies.
†See Test Your Word Score, page 523.

for the various age groups.

Differential Diagnosis

Pseudobulbar palsy is most infrequent in childhood under the age of seventeen years. When it is seen, one needs to consider only three major possibilities.

Diffuse Brain Damage of the Newborn

The newborn infant who manifests pseudobulbar palsy will have suffered brain damage at birth. Inability to swallow and vocalize normally is evident, often associated with paresis, apathy and inability to thrive. When the picture is complete it offers little diagnostic challenge. No therapy is available other than maintaining nourishment and preventing aspiration. The palsy may improve gradually and little evident residual may remain as the child matures.

Subacute Bacterial Endocarditis

Multiple cerebral emboli secondary to subacute bacterial endocarditis may result in bilateral vascular lesions and produce this syndrome in the younger age group. The frequency is not great and the diagnosis not difficult. The obvious signs of more gross neurological deficit are invariably present, especially bilateral pyramidal signs of mild to severe degree. The obvious cardiac pathology on auscultation and by history is present. Fever, systemic debility and cutaneous signs of emboli are evident. The therapy in these cases is important and dependent on an accurate diagnosis. The prognosis for these young brains is good, and remission of the pseudobulbar palsy is to be expected.

Disseminated Sclerosis

The occurrence of severe demyelinating disorders in the age group under seventeen years is rare. The appearance of a classical pseudobulbar palsy of insidious onset strongly suggests this disorder. The classical remission and exacerbation of multifocal neurological deficit should be evident by history. A careful neurological examination should reveal signs of other than the bulbar palsy, especially signs of incoordination, of pyramidal dysfunction, of impaired dorsal column function and of medial longitudinal fascicular dysfunction (a failure of the eyes to move conjugately).

Differential in Early Adulthood

The occurrence of pseudobulbar palsy in the young adult (18-50 years) is relatively common, but invariably due to the following three conditions.

Multiple Sclerosis

The greatest number of classical pseudobulbar palsy cases seen in this age will be secondary to advanced forms of multiple sclerosis, with the diagnosis usually evident from the associated neurological deficits. The history of remissions and exacerbations of multi-focal neurological deficits which have had their onset between the ages of 17 and 35 will be noted in most cases. This form of pseudobulbar palsy often shows associated hyperemotionalism; spon-

taneous laughter is common and may be most prominent. Present-day therapy of this disorder does little to alter the pseudobulbar symptomatology.

Meningoencephalitis

The classical form of pseudobulbar palsy may occasionally be seen in meningoencephalitis. The condition is diagnosed and treated, and only following the recovery from coma does the pseudobulbar palsy become evident. Some degree of spastic quadriparesis or hemiparesis usually persists. The course of the pseudobulbar palsy is that of all post-infectious neurological deficits—one of gradual improvement.

Intoxication

A form of pseudobulbar palsy is occasionally encountered in younger individuals who are under therapy with phenothiazines or reserpine. The patient with this pseudobulbar picture has the "gaping mouth," sialorrhea and slurring dysarthria and frequently manifests gross parkinsonian rigidity. Emotional lability is usually absent. These individuals walk with little neck movement and with loss of associated arm movement. This particular disorder can interfere with normal swallowing and may require the discontinuance of these medications. The symptomatology subsides following the cessation of therapy.

Differential in Older Age

Classical pseudobulbar palsy with emotional lability is commonly encountered after fifty years.

Bilateral Cerebrovascular Infarction

This is the most common cause of pseudobulbar palsy. It occurs suddenly in these people. The loss of ability to swallow and speak will coincide with the onset of a hemiplegia or hemiparesis which may vary in degree but will be evident if searched for. Others may have only a hemisensory defect from involvement of the thalamoparietal radiations, but this too represents a recent hemispheral "stroke." These patients have had previous involvement of the other hemisphere of their brain by small or large infarctions, often "silent." The opposite corticobulbar tract must have had previous damage, as pseudobulbar palsy does not occur as long as one corticobulbar tract is working. Neurological examination will invariably show the recent site of cerebral infarct involving the motor-sensory-visual pathways of one hemisphere and will demonstrate some mild signs of corticobulbar-corticospinal involvement from the opposite hemisphere, sometimes only a suggestively positive toe sign on the appropriate side. This condition occasionally requires dramatic measures such as tracheotomy to prevent aspiration of secretions. Intubation for maintenance of nourishment and even gastrostomy may be required during the acute phase. The signs of pseudobulbar palsy follow the course of vascular pathology and gradual improvement occurs. The bulb compensates well, so that most patients are again able to eat and drink adequately within the first ten days. The hyperemotionalism which is most severe in the early stages subsides and is frequently of little significance after the second or third month.

Conclusions

The recognition of classical pseudobulbar palsy is quite simple. Familiarity with a differential diagnosis will aid in its accurate diagnosis and prognostication.

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Steinbrocker's Syndrome*

This reflex dystrophy is characterized by a painful incapacity involving the shoulder, arm, hand, and fingers unilaterally with associated edema and circulatory and trophic disorders. The elbow joint is usually not involved. Steinbrocker and associates described the condition in 1948 and suggested the term "shoulder-hand syndrome."

The clinical picture varies in individuals, both in duration and in symptomatology. In general there are three stages in the course of the syndrome. The first stage, which usually lasts from three to six months, is characterized by pain and stiffness in the shoulder with subsequent involvement of the homolateral hand and fingers. Swelling of the hand makes closure painful and incomplete. In the second phase there may be a decrease in the shoulder pain and swelling of the hand, but increasing stiffness and flexion deformity of the fingers occur. Atrophy of the hand muscles and subcutaneous tissues becomes evident. Roentgenographic studies reveal evidence of osteoporosis. In the third stage irreversible changes become evident. These include contractures and subluxations, marked trophic changes, diminished blood flow in the extremity, and a drop in skin temperature.

This syndrome may occur after myocardial infarction or in association with a variety of other conditions including acute calcific tendinitis, trauma, hemiplegia, panniculitis, diffuse vasculitis, or cervical osteoarthritis. The disability is thought to be a reflex neurovascular dystrophy in which both the vasomotor and trophic symptoms are presumably due to reflex stimulation of the sympathetic nerve supply.

In many patients the condition remains essentially unchanged despite therapy, or shows gradual progression. Relief may sometimes be obtained by prolonged steroid therapy, procaine block of the stellate ganglion, or deep x-ray therapy over the shoulder area. Local injection of procaine and hydrocortisone into shoulder tissues may afford relief, especially if calcific tendinitis is present. In severe cases periarterial sympathectomy or ganglionectomy may be indicated.

Durham, Robert H.—Encyclopedia of Medical Syndromes
Hoeber Medical Division, Harper and Row, New York

See page 507.

Loneliness

Like most self-sufficient men, he was a lonesome man. It is the dependent people who find friends.—Arthur Hopkins

I love my family.
I adore this house.
My in-laws are great.
The neighbors are wonderful.



Indications. For use in management of anxiety and tension occurring alone or as accompanying symptom complex to medical and surgical disorders and procedures. Though not a hypnotic, fosters normal sleep through antianxiety and related muscle-relaxant properties.

Contraindications. History of sensitivity to meprobamate.

Important Precautions. Carefully supervise dose and amounts prescribed, especially for patients prone to overdose themselves. Excessive prolonged use has been reported to result in dependence or habituation in susceptible persons, as alcoholics, ex-addicts, and other severe psychoneurotics. After prolonged excessive dosage, reduce dosage gradually to avoid possibly severe withdrawal reactions. Abrupt discontinuance of excessive doses has sometimes resulted in epileptiform seizures.

Warn patients of possible reduced alcohol tolerance, with resultant slowing of reaction time and impairment of judgment and coordination.

Reduce dose if drowsiness, ataxia or visual disturbance occurs; if persistent, patients should not operate vehicles or dangerous machinery.

Side Effects include drowsiness, usually transient; if persistent and associated with ataxia, usually responds to dose reduction; occasionally concomitant CNS stimulants (amphetamine, mephentermine sulfate) are desirable. Allergic or idiosyncratic reactions are rare, but such reactions, sometimes severe, can develop in patients receiving only 1 to 4 doses who have had no previous contact with meprobamate. Previous history of allergy may or may not be related to incidence of reactions. Mild reactions are characterized by itchy urticarial or erythematous maculopapular rash, generalized or confined to groin. Acute nonthrombocytopenic purpura with cutaneous petechiae, ecchymoses, peripheral edema and fever have been reported. One fatal case of bullous dermatitis following intermittent use of meprobamate with prednisolone has been reported. If allergic reaction occurs, meprobamate should be stopped and not reinstituted. Severe reactions, observed very rarely, include angioneurotic edema, bronchial spasms, fever, fainting spells, hypotensive crises (1 fatal case), anaphylaxis, stomatitis and proctitis (1 case) and hyperthermia. Treat symptomatically as with epinephrine, antihistamine and possibly hydrocortisone. Aplastic anemia (1 fatal case), thrombocytopenic purpura, agranulocytosis and hemolytic anemia have occurred rarely, almost always in presence of known toxic agents. A few cases of leukopenia, usually transient, have been reported on continuous administration.

Meprobamate may sometimes precipitate grand mal attacks in patients susceptible to both grand and petit mal. Extremely large doses can produce rhythmic fast activity in the cortical pattern. Impairment of accommodation and visual acuity has been reported rarely. After excessive dosage for weeks or months, withdraw gradually (1 or 2 weeks) to avoid recurrence of pretreatment symptoms (insomnia, severe anxiety, anorexia). Abrupt discontinuance of excessive doses has sometimes resulted in vomiting, ataxia, tremors, muscle twitching and epileptiform seizures. Prescribe very cautiously and in small amounts for patients with suicidal tendencies. Suicidal attempts have resulted in coma, shock, vasomotor and respiratory collapse and anuria. Excessive doses have resulted in prompt sleep, reduction of blood pressure, pulse and respiratory rates to basal levels, and occasionally hyperventilation. Treat with immediate gastric lavage and appropriate symptomatic therapy. (CNS stimulants and pressor amines as indicated). Doses above 2400 mg./day are not recommended.

Composition. Tablets, 200 mg. and 400 mg. meprobamate. Coated Tablets, WYSEALS® EQUANIL (meprobamate) 400 mg. (All tablets also available in REDIPAK® [strip pack], Wyeth.) Continuous-Release Capsules, EQUANIL L-A (meprobamate) 400 mg.

The young homemaker: her underlying anxiety and tension can surface and intensify under the continuous stress of rearing a growing family. Especially when she's confined to the home and its environs so much.

You can help her over the rough spots with reassurance and counsel. Equanil can help relieve tension, ease anxiety—with little risk of serious side effects. Time and experience will probably do the rest.

Equanil®
(meprobamate)

Wyeth Laboratories
Philadelphia, Pa.

Photo professionally posed.



Alcoholism

Chemical Patterns of 500 Alcoholics*

Richard L. Reece, M.D.
Minneapolis, Minnesota
Marwood E. Wegner, M.D.
St. Croix Falls, Wisconsin

"An alcoholic is someone who drinks more than I do."
An Anonymous Nonalcoholic,
by his own definition
"Moderation is a fatal thing. Nothing succeeds like excess."
Oscar Wilde
A Woman of No Importance III

IN THE OPENING QUOTES two wags were being flippant. Yet they made their points. Take the comment of the "nonalcoholic". Some 70 percent of American adults drink. About one of 15 of these drinkers is an alcoholic, and there are about 6.5 million alcoholics in the United States.[1] Given these statistics, who is to say who drinks enough to be classified as an alcoholic. Indeed, even friends, neighbors, and relatives are reluctant to admit a person might fall into the dreaded category.

The second quote, though perversely twisted, is apropos, too. For alcoholics admitted to private hospitals are often successful citizens, not grizzled derelicts. Typically, these alcoholics are married, own a respectable home, have a good job record, and participate in church or lodge activities.[2] True, lower-class citizens are more likely to have cirrhosis and to die of their alcoholism, but the fact remains that alcoholism is common among the well-to-do.

Alcoholism is no laughing matter. As it stalks through the land, it leaves in its wake divorces, ruined careers, delinquents, disease, and death. It ranks as the fourth or fifth leading cause of death in persons over 40,[3] costs society more than two billion dollars a year,[4] and is the fourth most common problem seen by physicians in their offices.

Diagnostic Problems

Alcoholism assumes many guises, such as gastritis, peripheral neurologic deficits, pancreatitis, cirrhosis, fatty liver, convulsions, heart failure, psychologic dependency, and psychosis—a wide enough array of physical and mental states to boggle the most astute diagnostician. To muddle matters more, patients tend not to admit they drink excessively. And why should they? After all, our society condemns alcoholism. Besides, they may not even be aware that they drink beyond control. And, as you know, alcoholics may have few symptoms or signs. But they may have certain telltale serum chemical changes. Thereby hangs the tale we shall try to tell.

The Study

As patients entered the treatment center, physicians there filled out the questionnaire below. Blood was then drawn, centrifuged, and sera was sent to us to be run on a Sequential Multiple Analyser December, 1960.

Questionnaire

Date.....
Name..... Sex..... Age.....
Occupation .....
Duration of Alcoholism.....
Days since last drink.....
Daily .....
Periodic .....
Drugs past 2 weeks.....
.....
.....
.....
Withdrawal Symptoms .....
Liver Palpable .....

Table 1 summarizes the questionnaire data.

This tabulated summary reveals a great deal about the people we screened. Four of five, for example, were men. This jibes with reports from other centers for alcoholism, though the true ratio of men to women may be closer than 2 to 1, since women tend to be more secretive about their drinking. The summary also indicates that alcoholism tends to become manifiest in the forties; that men start drinking earlier, are more likely to imbibe daily, are less likely to be on tranquilizing drugs, are more likely to be suffering pangs of withdrawal, and are more likely to have palpable livers.

Abnormal Tests

And what about the number of abnormal tests? First, 165 patients had normal graphs.

*Conducted under the auspices of Hazeldon Rehabilitation Center for Alcoholism and members of the St. Croix Falls Clinic.

TABLE 1
Summary of Results Obtained by Questionnaire

Date of study—July 1, 1969 to November 1, 1969

Sex—400 men, 100 women

Age—Mean age of men 46 years
Mean age of women 44 years

Duration of alcoholism
Mean duration, men, 17 years
Mean duration, women, 10 years

Occupation, mostly middle or upper class white collar or professional people

Days since last drink
Mean, 1.6 days for men
Mean, 5.0 days for women

Drinking habits
77 percent of men drank daily
61 percent of women drank daily

Drugs—mostly tranquilizers
40 percent of men on drugs
80 percent of women on drugs

Withdrawal symptoms
40 percent of men
25 percent of women

Palpable livers
31 percent of men
15 percent of women

This means, of course, that this type of chemical screening is not a sure-fire way to unmask alcoholism. But 335 alcoholics did have abnormal graphs. When we say "abnormal graphs we are referring to abnormalities in these tests—high uric acid, high total protein, low albumin, high bilirubin, high alkaline phosphatase, high lactic dehydrogenase, and high serum glutamic oxalo-acetic transaminase. We arrived at my criteria for normal by taking SMA-12/60 chemistry graphs from 1000 consecutive office patients, calculating the range on probability paper (Number 46-8000 from Keuffel and Esser), discarding values falling outside that range, then recalculating the ranges on probability paper again. This technique is described in an earlier paper.[6] In Table 2, we list percent of abnormal tests.

Observations

As you can see from Table 2, an abnormal SGOT sensitivity indicates alcohol liver damage. Rubin and Lieber have noted that SGOT levels rise significantly after a normal person ingests moderate amounts of alcohol.[7] And one of the clues to alcoholic hepatitis is a SGOT of 50 to 200 units. In our patient group, those

TABLE 2
Percent of Abnormal Tests in 500 Alcoholics

Tests	Upper or Lower Limits	Percent Abnormal Men	Women
High Uric Acid	Men—7.9 mg% Women—6.6 mg%	15%	16%
High Total Protein	Men—7.9 mg% Women—7.8 mg%	7%	8%
Low Albumin	Men—3.0 mg% Women—2.9 mg%	1%	1%
High Bilirubin	Men—1.0 mg% Women—1.0 mg%	28%	10%
High Alkaline P'tase	Men—84 mU/ml Women—81 mU/ml	17%	16%
High LDH	Men—197 mU/ml Women—193 mU/ml	13%	8%
High SGOT	Men—39 mU/ml Women—34 mU/ml	68%	52%

with palpable livers had a mean SGOT of 82 mU/ml, while those with livers not felt by examiners had a mean SGOT of 62 mU/ml. The other two enzymes, LDH and alkaline phosphatase, proved to be less sensitive indicators of hepatic damage. No statistical difference existed in levels of the two enzymes in patients with palpable and nonpalpable livers. Few patients had serum protein changes—a state of affairs you might expect since only 10 patients were said by examiners to have overt cirrhosis.

Relation of Abnormal Tests to Recent Drinking and Duration of Drinking

Uric acid elevations occurred most often in those drinking up to the day of or the day before admission. Sixty percent of the patients fell in this category, yet this group had 93 percent of high uric acids. This supports Lieber and his associates' observation that significant hyperuricemia occurs in intoxicated alcoholics and in chronic alcoholics given alcohol.[8] This high incidence of abnormal tests in actively drinking alcoholics was true of other tests, too. For example, those drinking within 48 hours of admission had 78 percent of high SGOT's, 89 percent of elevated bilirubins, 91 percent of elevated LDH's, and 79 percent of high alkaline phosphatases. (See Table 3 for relation of mean values to recent drinking.) The duration of alcoholism had less to do with the number of abnormal tests. Of those dating

TABLE 3
Relation of Mean Values of Chemistry Graph Tests to Recent Drinking

Mean values when patient's last drink on	SGOT	Bilirubin	Alk. P'tase	LDH	Uric Acid
Day of admission	77 mU/ml	1.0 mg%	69 mU/ml	161 mU/ml	6.6 mg%
Day before admission	65 mU/ml	0.9 mg%	67 mU/ml	163 mU/ml	6.0 mg%
2 to 5 days before	54 mU/ml	0.6 mg%	55 mU/ml	135 mU/ml	5.6 mg%
6 to 10 days before	44 mU/ml	0.5 mg%	65 mU/ml	146 mU/ml	5.2 mg%
11 to 15 days before	38 mU/ml	0.5 mg%	64 mU/ml	147 mU/ml	5.2 mg%
15 to 30 days before	36 mU/ml	0.7 mg%	64 mU/ml	132 mU/ml	5.1 mg%
More than 30 days before	24 mU/ml	0.6 mg%	56 mU/ml	127 mU/ml	4.8 mg%

their alcoholism less than 10 years, 65 percent had one or more abnormal tests; of those who traced their alcoholism back between 10 and 20 years or over 20 years, the figures were 64 percent and 72 percent respectively.

What does this all mean? It means to us that the alcoholic that has abstained for several days has ebbing of his liver damage, that the actively drinking alcoholic will show active damage, that chemistry graphs tend to reflect acute liver injury, and that, in this group of alcoholics at least, liver injury is reversible and not necessarily cumulative.

Chemical Patterns

If liver injury can be reversed by stopping drinking, then it ought to be worthwhile to screen for alcoholics with chemical tests. To detect the drinker (who, of course, isn't necessarily an alcoholic), we believe physicians ought to look for certain patterns in chemistry graphs. We prefer to think of these patterns in terms of single abnormal tests or pairs of abnormal tests. Except for a solitary elevation of SGOT, for instance, it is unusual for an alcoholic to have an elevation of a single test (Table 4).

TABLE 4
Number and Percent of Solitary Test Elevations

Test	Number	Percent
SGOT	103	20.6%
Alk. P'tase	21	4.2%
Uric Acid	12	2.4%
Bilirubin	8	1.6%
LDH	6	1.2%
Total Protein	3	0.6%

Simplifying Interpretation

To simplify interpretation of other patterns, we try to think in terms of paired abnormal tests. Not that three or more abnormal tests don't occur. They do. Sixty-five patients in this series had three or more abnormal tests, the most frequent combinations being ↑bilirubin, ↑alkaline phosphatase, and ↑SGOT (13 patients); ↑uric acid, ↑bilirubin, ↑SGOT (12 patients).

Why pairs of abnormal tests? It is simply easier to juggle mentally. In Table 5, we list the most commonly paired abnormal tests.

TABLE 5
Number of Patients in Which One Test Occurred in Combination with Another Abnormal Test

SGOT Pairs		*Bilirubin Pairs*		*Alk. P'tase Pairs*	
with bilirubin	104	with SGOT	104	with SGOT	48
with alk. p'tase	60	with alk. p'tase	28	with bilirubin	28
with uric acid	45	with uric acid	22	with T. Protein	12
with LDH	44	with LDH	23	with LDH	8
with T. Protein	20	with T. Protein	13	with uric acid	7
LDH Pairs		*T. Protein Pairs*		*Uric Acid Pairs*	
with SGOT	44	with alk. p'tase	28	with SGOT	44
with bilirubin	23	with SGOT	20	with bilirubin	22
with uric acid	15	with bilirubin	13	with LDH	15
with alk. p'tase	8	with LDH	7	with alk. p'tase	7
with T. Protein	3	with uric acid	3	with T. Protein	3

Note the frequency of these combinations. By keeping an eye out for them, you may be able to diagnose or suspect occult alcoholism more often.

References may be secured from the author.

The Ailments of Men in History

Dr. Johnson's Stroke

Samuel Johnson (1709-1784) was evidently very fond of eating; himself, he boasted of his delicate tastes in food; and when he ate, "the veins of his forehead stood out and a strong perspiration was visible." Presumably when Boswell said "the veins of his forehead" he meant the superficial temporal arteries, for if they had been the soft and thin-walled veins, Johnson, bestrewn with bladders, would have looked indeed noteworthy. But there came a time when they stood out once too often, and probably they never shrank back again to the normal size, but became thickened. Thus his blood-pressure rose under the strain of arteriosclerosis and in the course of years the inevitable results of gluttony overtook him. Drink, guzzle, and syphilis are the three deadly sins, and they are deadly in proportion to the effect that they cause upon the arteries.

Warnings came in 1782 with breathlessness and pain in the chest; the heart was evidently beginning to rebel, but the first real alarming warning came on the night of June 17th, 1783, when he awoke in the middle of the night and found that he could not speak. Trying to write, he found that "my hand made wrong letters," that is to say he had not only aphasia, but "agraphia" or loss of power to write.

The exact lesion would appear to have been that one of the cerebral arteries that supplied the left side of Johnson's brain had for some reason been thrown into a state of spasm, and caused temporary softening of the brain owing to interference with its blood-supply. If an artery had actually burst on the site of a tiny aneurysm, the old man would not have recovered so soon, even temporarily.

Johnson's terror led him to write a prayer for his recovery, done in Latin verse. "The lines were not very good, but I knew them to be not very good, so concluded that I was not impaired in my faculties." There you see at once the supreme passion of the man—Learning—coming out in what he thought to be the very article of death.

Then, "in order to rouse the vocal organs, I took two drams. Wine has been celebrated for the production of eloquence, so I put myself into violent motion and I think repeated it; but all was in vain." Not that it made much difference; Death was focusing his eyes on Dr. Johnson; the call was coming, and no earthly power could avert it.

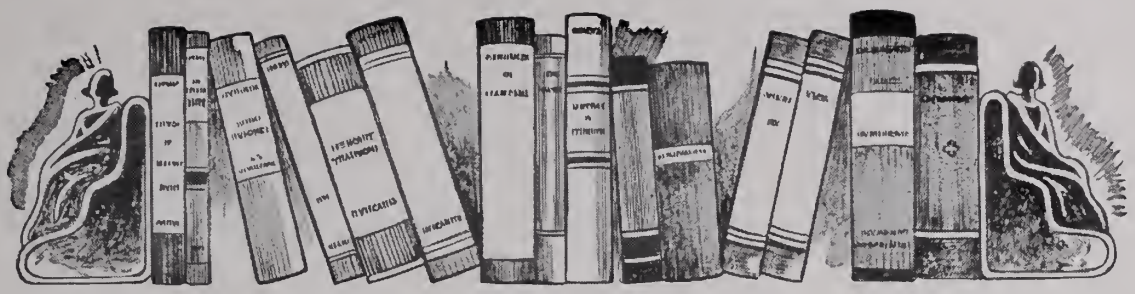
After the paralytic stroke all the devils in hell seem to have settled upon the poor old gentleman, with their gout, dropsy, and continual fear of death . . . And his cough became exceedingly troublesome, possibly due to congestion of the base of his lungs that would be caused in a way much the same as caused the dropsy; he was becoming "water-logged."

A rather remarkable thing is that, once having become filled up with dropsy, he got rid of it apparently suddenly. If I remember rightly Dr. Johnson was taking squills at the time, and squills is still used for getting rid of fluid from the body, though it has been supplanted by more efficient drugs. One might perhaps think that hope told Johnson a flattering tale, but he says expressly that he got rid of twenty pints. Queer things happen in dropsy, and even such a pseudo-miracle as Johnson's is not unknown.

His actual end seems to have been caused by a mild terminal pneumonia, which in a healthy young person would have been thrown off like a cold in the head; but was too much for ancient lungs and tired heart.*

Editor's Note: With all his sins and all his virtues, seventy-five must have been a ripe old age in those days.

*Post Mortems of Mere Mortals by C. MacLaurin, 1925.



Book Reviews

Sleep over books, and leave mankind unknown.—Charles Churchill.

ESSENTIALS OF GASTROENTEROLOGY, J. Ned Smith, Jr., MD.; Publisher: The C. V. Mosby Company, St. Louis, Missouri. Price: $14.75.

This book is an outgrowth of a mimeographed outline of lectures. Thus it is written primarily for undergraduate medical students. With a background of private practice in gastroenterology and as an academic teacher the author sees a need to fill a void left by the disappearance of formal lectures.

The importance of increased bile and urobilinogen levels in urine and feces is discussed at length; however, the author fails to mention the importance of the absence of urobilinogen in the stool or urine. In discussing acute colicystitis, it is said, "The imprisoned bile has a direct toxic effect on the gall bladder." I question this unsupported statement. In discussing diverticulitis the student is advised that, "Surgery will rarely be necessary to stop massive bleeding." I hate to think of the consequences if students should elect to use this book as their therapeutic guideline in practice. The radiological features of diverticulitis versus carcinoma of the sigmoid colon are neatly discussed; however, the student is not told the practical if's and when's of barium contrast studies of the colon. While the fascinating features of the carcinoid syndrome are described and discussed at great length, I fail to find any mention of the outcome of the disease. While carcinoma of the liver, the gall bladder, the bile ducts and the pancreas are discussed at length, cancer of the ampulla of Vater is mentioned in only one sentence.

In spite of its shortcomings this outline on problems in gastroenterology has retained some of the charms which it undoubtedly had when given as a lecture series. On many occasions the author interrupts himself to quote extensively from masters in the field. His literature references are extensive and at times date up to 1966. However, in spite of these positive points the book falls short of its aim to be a guideline to the undergraduate student of gastroenterology.

H. W. Heupel, M.D., Ph.D.
Minneapolis, Minnesota

MASTERS OF MEDICINE, J. Arthur Myers, M.D.; Publisher: Warren H. Green, Inc., St. Louis, Missouri; Pages: 921; Price: $12.75.

This historical sketch of the College of Medical Sciences, University of Minnesota, covers a span of 80 years. It has been a prodigious undertaking by a man who was well qualified to do it.

The numerous historical biographies are pertinent to the life of these individuals during their active career. Their factual nature should make them suitable as reference material for anyone who is interested in obtaining a short biography of his favorite professor.

This book is well bound and the type faces can be read with comfort.

From the histories of these medical men it is readily understood why Minnesota has become one of the great medical centers of the world.

Carl O. Rice, M.D.
Minneapolis, Minnesota

MEASUREMENT IN EXERCISE ELECTROCARDIOGRAPHY. The Ernst Simonson Conference. Edited by Henry Blackburn. Charles Thomas. 1969 485 pp.

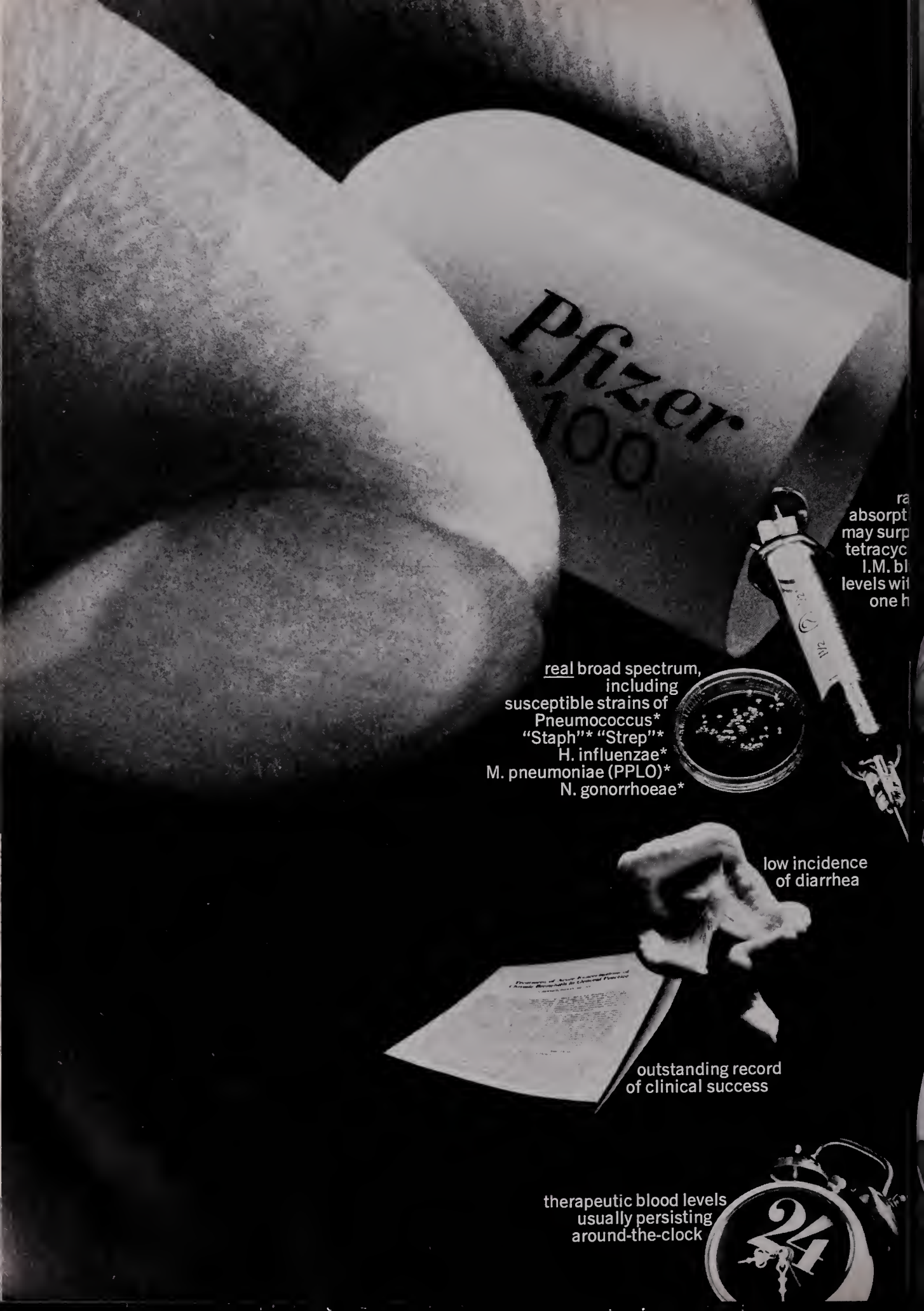
"Measurement in Exercise Electrocardiography" is essentially a Festschrift honoring Ernst Simonson in the year of his retirement from the faculty of the University of Minnesota (though definitely not retirement from his numerous other medical and physiological activities). In September 1968 a distinguished group of physicians, physiologists, mathematicians, and engineers gathered in Minneapolis, and this book is edited from the tapes recorded at the meeting.

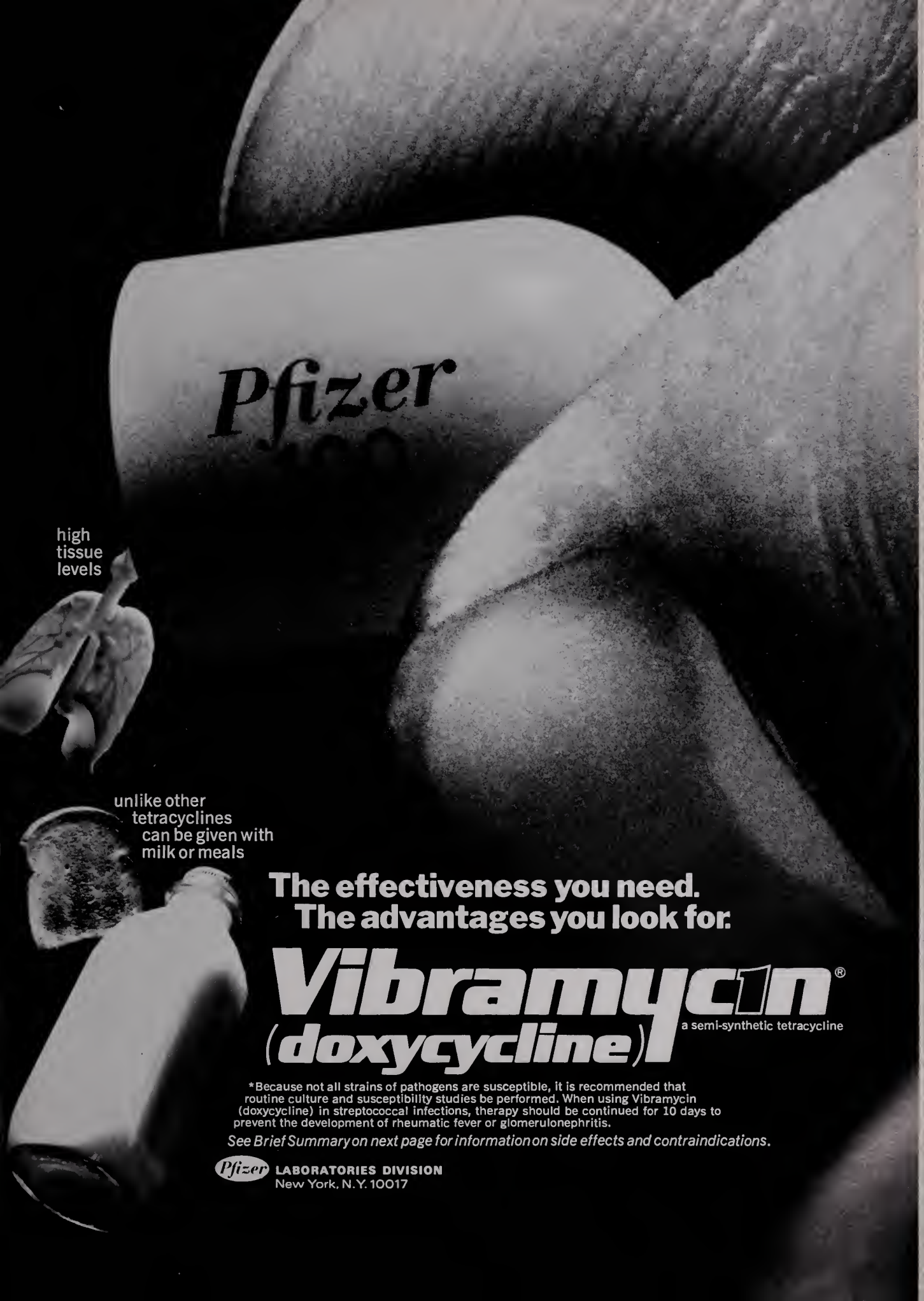
It is evident from many different chapters that measurement nowadays implies automated measurement, that is, computer study. For example, in order to measure a wave form, the "noise" level must be minimized. These methods are discussed by several bio-engineers, especially by Otto Schmitt.

In 1944 Ernst Simonson left his post at the Mount Sinai Hospital in Milwaukee and came to Minneapolis to join Ancel Keys at the Laboratory of Physiological Hygiene. When Mount Sinai of Minneapolis opened its doors in 1951, Dr. Simonson was invited to become a consultant in electrocardiology, a position he still holds. A fascinating chapter is his recital of the vicissitudes of his life as a German trained scientist who worked in Russia and was offered there the highest academic position, who left Russia one jump ahead of Stalin's OGPU, and who was offered a similar position in the late thirties in Paris. Luckily he opted for life in America at that time with no certainty of a position.

A small demerit of the book is the direct transcription of the spoken "speech" to the written word. It is preferable to ask discussants to write the chapter even though, as every Festschrift organizer knows, it is easier to get a speech made than a paper writ.

Reuben Berman, M.D.
Minneapolis, Minnesota


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"Staph"* "Strep"*
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M. pneumoniae (PPLO)*
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therapeutic blood levels
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24



The effectiveness you need.
The advantages you look for.

Vibramycin® (doxycycline)

a semi-synthetic tetracycline

*Because not all strains of pathogens are susceptible, it is recommended that routine culture and susceptibility studies be performed. When using Vibramycin (doxycycline) in streptococcal infections, therapy should be continued for 10 days to prevent the development of rheumatic fever or glomerulonephritis.

See Brief Summary on next page for information on side effects and contraindications.

Pfizer LABORATORIES DIVISION
New York, N.Y. 10017



and convenience too.

The unique new Vibramycin (doxycycline) V-Pak is especially convenient for use both in your office practice and in the hospital outpatient department. It contains a typical four-day course of therapy for routine infections with easy-to-understand patient instructions. The dosage is low, just 100 mg. b.i.d. the first day followed by 100 mg. once a day for the next three days. In more severe infections, 100 mg. q.12 h. is recommended. If renal impairment exists, lower than usual doses are indicated.

And for added convenience in the hospital pharmacy, Vibramycin is available in unit-dose packs of 100 (10 x 10's) for both the 100 mg. and the 50 mg. capsules.

VIBRAMYCIN® (doxycycline)
BRIEF SUMMARY

Contraindicated: In individuals who have shown hypersensitivity to doxycycline.

Warnings: The usual dosage and frequency of administration of Vibramycin (doxycycline) differs from those of other tetracyclines. Exceeding the recommended dosage may result in an increased incidence of side effects.

If renal impairment exists, even usual doses may lead to excessive accumulation of the drug and possible hepatic toxicity. For such patients, lower than usual doses are indicated and, if treatment is prolonged, Vibramycin serum level determinations may be advisable.

Vibramycin, like other tetracyclines, may form a stable calcium complex in any bone-forming tissue, although *in vitro* Vibramycin binds calcium less strongly than other tetracyclines. The use of Vibramycin during tooth development (last trimester of pregnancy, neonatal period, and early childhood) may cause discoloration of the teeth (yellow-gray-brownish). This effect may occur mostly during long-term use, but also may occur with short-treatment courses.

Increased intracranial pressure with bulging fontanelles has been observed in infants receiving tetracyclines. This effect has disappeared rapidly on cessation of therapy with no sequelae.

In certain hypersensitive individuals treated with Vibramycin, exposure to direct sunlight may precipitate a photodynamic reaction. In individuals with a history of photoallergic reactions to tetracyclines, exposure to direct sunlight should be avoided and treatment should be discontinued at first evidence of skin discomfort.

Precautions: As with any antibiotic, overgrowth of nonsusceptible organisms may occasionally occur. Constant observation of the patient is essential. If such superinfections are encountered, Vibramycin should be discontinued and replaced by appropriate therapy.

When treating gonorrhea in which lesions of primary or secondary syphilis are suspected, proper diagnostic procedures, including dark-field examinations, should be utilized. In all cases in which concomitant syphilis is suspected, monthly serological tests should be made for at least four months.

Adverse Reactions: Nausea, vomiting, diarrhea, vaginitis, as well as reactions of an allergic nature such as dermatitis, urticaria, and anaphylaxis may occur but are rare. Glossitis, stomatitis, proctitis, onycholysis and discoloration of the nails may rarely occur during tetracycline therapy as with other antibiotics. If severe adverse reactions, individual idiosyncrasy, or allergy occur, discontinue medication.

As with other tetracyclines, elevation of SGOT or SGPT values, or elevated BUN have been reported, the significance of which is not known at this time. Anemia, neutropenia, and eosinophilia have been reported, as with other tetracyclines.

Animal Pharmacology: As with other tetracyclines, at doses greater than those recommended for human usage, Vibramycin produces discoloration of animal thyroid glands. Careful monitoring of animals and humans has disclosed no abnormalities of thyroid function studies. Also, as with other tetracyclines, at relatively high oral doses, evidence of hepatotoxicity has been noted in dogs and signs of gastrointestinal intolerance have been seen in both dogs and monkeys.

Dosage: The usual dose of Vibramycin is 200 mg. on the first day of treatment (administered 100 mg. every 12 hours) followed by a maintenance dose of 100 mg./day. The maintenance dose may be administered as a single dose, or as 50 mg. every 12 hours. In the management of more severe infections (particularly chronic infections of the urinary tract), 100 mg. every 12 hours is recommended. The recommended dosage schedule for children weighing 100 pounds or less is 2 mg./lb. of body weight divided into two doses on the first day of treatment, followed by 1 mg./lb. of body weight given as a single daily dose or divided into tw doses, on subsequent days. For more severe infections up to 2 mg./lb. of body weight ma be used. For children over 100 lbs. the usual adult dose should be used.

Acute gonococcal anterior urethritis in males —a single dose of 300 mg. or 100 mg. b.i.d. for 2-4 days.

Acute gonococcal infections in the adult fema should be treated with doses of 100 mg. b.i.d. until cure is effected.

Therapy should be continued beyond the time that symptoms and fever have subsided. When used in streptococcal infections, therap should be continued for 10 days to prevent the development of rheumatic fever or glomerulonephritis.

If gastric irritation occurs, it is recommended that Vibramycin be given with food or milk. Studies indicate that the absorption of Vibramycin is not markedly influenced by simultaneous ingestion of food or milk.

Simultaneous administration of aluminum hy droxide gel given with tetracycline antibiotics including Vibramycin has been shown to decrease absorption.

Supply: Vibramycin Hyclate (doxycycline hyclate) is available as capsules containing doxycycline hyclate equivalent to 50 mg. of doxycycline, bottles of 50, unit-dose pack of 100 (10 x 10's), and X pack of 50 (5 x 10's); capsules containing doxycycline hyclate equivalent to 100 mg. of doxycycline, bottles of 50, unit-dose pack of 100 (10 x 10's and V pack of 25 (5 x 5's).

Vibramycin Monohydrate (doxycycline monohydrate) is available as a dry powder for oral suspension containing when reconstituted doxycycline monohydrate equivalent to 25 mg of doxycycline per 5 cc. (each teaspoonful), with a pleasant-tasting raspberry flavor, 2 oz. bottles.

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(doxycycline)

a semi-synthetic tetracycline

Special Article

Medical Care in Vietnam

Kristofer Hagen, M.D., Edina, including an interview with
Robert H. Monahan, M.D., St. Paul.

As the 416th American Volunteer Physician for Vietnam I have just finished sixty days of fascinating medical work at a provincial hospital in the delta area of the world's most troubled country. Approximately three months after my first inquiry, I was accepted, ticketed, certified, processed, immunized, briefed and ready for action along with six other American doctors. Every two weeks a similar group arrives in Saigon.

It was my good fortune to be assigned to the Phu Vinh Hospital located southeast of Saigon. As I scrambled out of the whirling Army helicopter and jeeped to my quarters late one afternoon, I found a town of 38,000 in which barbed wire, sandbag bunkers and bombed-out buildings had not entirely erased the charm of its lovely streets lined with trees and flowers. The people seemed glad to see another American "Bac Si" (doctor). The 350-bed Phu Vinh Hospital has to supervise the health needs of about 385,000 people in this province. Guerilla warfare in Vietnam has now for some time produced a steady flow of casualties all over the country, and these, plus the usual run of medical, surgical and obstetrical conditions in a provincial hospital, cannot be handled adequately by the greatly decimated Vietnamese medical personnel. They much appreciate and need the help given by Americans. Medical supplies come entirely through Vietnamese channels, but are practically all from American sources. The administrative responsibilities are sometimes hard to define as the American team is supposed to be purely *advisory*, not actually in charge. This can be awkward, especially when American funds are to be used for needed hospital improvements or equipment. I was impressed by the patience and diplomacy of the four doctors of our MILPHAP team in this regard, as well as by their medical and surgical ingenuity, resourcefulness and diligence. One of the men had done a year in surgery at the Mayo Clinic, another had just qualified as a pediatrician, the others were recently out of internships.

They put me in charge of a male surgical and medical ward and later of a female medical ward, so I saw and treated a wide variety of conditions. Casualties from Viet Cong attacks or mines comprised at least 85% of our surgery and could come at any hour of the day. Because of curfew regulations and uncertain security in the area, as well as the lack of nursing services or x-ray after four p.m., all casualties coming in after that hour were not treated by us, but were handled by the *Medicine de Chef*. I filled the hour between four and five by teaching a class in conversational English. Since Viet Cong activity was usually at night, most casualties appeared at the hospital in the morning or during the day.

My ward handled almost every conceivable kind of orthopedic emergency

*Military Provincial Health Assistance Program

caused by shrapnel or gunshot wounds. Shattering compound fractures of hands, forearms, elbows, humeri, feet, legs, femurs, hips, mandibles, etc. were routine. One woman's humerus was split longitudinally by a bullet. We had a lot of below-the-knee amputations, a fair number of fingers and toes to amputate. Abdominal cases with perforated wounds of the large bowel requiring colostomy gave us the most trouble. Our most dramatic moments came from chest wounds requiring decompression of hemothorax or pneumothorax. I still remember one Saturday afternoon when the team was busy in our first operating room with a tough abdominal case and I had to handle singlehandedly in the other operating room, without a nurse or technician, a young Vietnamese soldier with a massive hemothorax from a left chest wound. The chest tube I inserted spurted out over a liter of blood in a few minutes, but water-sealed drainage, blood replacement, and antibiotics won the day.

Medical problems in such a hospital can be very challenging, if not frustrating. Limited laboratory and x-ray facilities, no electrocardiographic service, and the absence of other refined diagnostic tools can make your mind scramble for what you remember of physical diagnosis. Language barriers make history-taking slow and difficult. Nevertheless, we saw and treated reasonably adequately such varied conditions as hepatic amebiasis, various forms of tuberculosis, beri-beri hearts, leprosy, typhoid fever, malaria, hookworm infestations, pellagra, profound post-partum anemias, nephrosis, cirrhosis, even catatonic schizophrenia.

Side trips to visit other volunteer physicians and hospitals at Bac Lieu, Chau Doc, and Cantho provided pleasant and informative interludes in the two months I spent in Vietnam. A visit with Dr. Tom Mitchell of Vicksburg, Mississippi, a family doctor stationed at Bac Lieu, revealed that there they had a superior *Medicine de Chef* and a somewhat more sophisticated staff that ran the hospital more efficiently than ours. They had better nursing services, an active out-patient department, a good obstetrical and gynecological service with an American specialist in charge and even a going birth control clinic, inserting the loop in an ever increasing number of women. Most Vietnamese women are eager for such help and few, if any, want twenty pregnancies, as the mother of my interpreter had!

On my Bac Lieu trip I learned that the Viet Cong during Tet had occupied the entire hospital at Camau, routed the patients out, and destroyed the operating room suite, so that it had to be rebuilt entirely. I also talked with a Navy corpsman working out of Soc Trang who had charge of a number of outlying dispensaries and often had to assist the local midwives with difficult deliveries, even applying forceps, something he had never been trained to do! Such is rural Vietnam. From him I heard the strange tale of one *Medicine de Chef* who took a whole year to get over misunderstandings.

A most informative interview occurred in Cantho, IV Corps headquarters, with Dr. Robert Hugh Monahan of St. Paul, ophthalmologist who served concurrently with me his sixty-day tour in Vietnam. Excerpts from this interview follow:

Dr. Hagen:

Hello, Hugh, I just flew in from Phu Vinh and stopped over on my way to Chau Doc. It's mighty nice to meet a classmate from Minnesota out here. How are things at the headquarters hospital?

Dr. Monahan:

Hello and welcome! Here at Cantho Hospital as an ophthalmologist vol-

unteer physician from the American Medical Association. I've had a very good experience and am really delighted with the arrangements, though I realize that in time some changes could be made. I'm fortunate in that I have a counterpart, a Vietnamese ophthalmologist.

Dr. Hagen:

That's very encouraging. Would you tell us what types of eye diseases you have been treating here mostly?

Dr. Monahan:

When we started we were still getting the aftermath of the Tet offensive, so as a result a great deal of our work was treating serious injuries. It was interesting because almost all of the injuries to the eye and eyelids that we saw at that time were from four to ten days old. Consequently, everything we worked on was repaired secondarily. Gradually over the past six weeks there has been a change. We now find that injury cases are coming within four to six hours after injury, indicating that our security defense is far better in this area. Thus the injuries have a better hope of repair with a fair result. The hospital census as a whole still consists of about 90% injury cases, but on the eye service it is somewhat less than that. Currently, with the change in our general orientation and with the war moving farther away from us, we are seeing much more elective work. We're doing a lot of cataracts, a good deal of glaucoma surgery, and in our clinic of course we see a tremendous amount of glaucoma surgery, as one sees throughout Asia.

Dr. Hagen:

It's interesting that you see a lot of glaucoma. Is this in about the same age group as we have in the United States or does it occur here in younger people?

Dr. Monahan:

I would say in a somewhat younger age group. Glaucoma here is a very different disease from what it is in the United States. When we see glaucoma here the patient is already complaining of blurred vision. When we see it in the United States we usually see it because some doctor has checked the ocular tension and found it to be elevated. In other words, here the disease has already done a great deal of damage before it is diagnosed. Another complicating factor with glaucoma here is that most of the patients cannot afford medicine, so if we prescribe medicine there is a very good chance that the patient won't get it.

Dr. Hagen:

Have you enjoyed your stay in Vietnam and do you think the program here is worthwhile?

Dr. Monahan:

It's been a delightful experience. I wouldn't have missed it for anything. I think the MILPHAP teams and the Volunteer Physicians for Vietnam are doing a tremendous amount of good and that the country is going to advance a good deal in the near future.

Conclusion

I can say that all the volunteer physicians I have met agree that this program is necessary, worthwhile, and productive of good. It provides direct medical and surgical care to a very needy, war-stricken population which has only about one doctor of its own for 40,000 or more people. Our

military involvement in Vietnam is such that we have a moral responsibility to help care at least for the many wounded. While this is being done there is little time or energy left for up-grading the level of medical care in the country as a whole, though great progress has been made in the Saigon Medical School and in eye work, in spite of wartime conditions. If peace comes to Vietnam there will be a sharp decline in the number of civilian casualties and we shall have to ask ourselves how seriously we want to take the more enduring medical problems of Vietnam—or of all southeast Asia, for that matter. Assuming that the American taxpayer is willing to go on subsidizing with personnel and materiel complete medical care in a foreign country with which we have only transient emotional ties, we must make it clear that the job will take several decades of painstaking, dedicated work. Carefully selected, fewer and longer-term personnel, accompanied by families; improved training facilities for ancillary medical personnel in x-ray, laboratory, electrocardiography, nursing, and even housekeeping services; more efficient hospital administration; improved public health work and sanitary engineering—these and many other aspects of the problem have to be studied, planned and executed if we are to carry out the medical task we have started in Vietnam. Based on my observations, I would predict that this could become one of the finest contributions our American medical profession has made to world health.

Volunteer Physicians for Vietnam

Thirty-two physicians are needed every 60 days to keep hospital staffs at full strength. This is a challenge to American physicians. Expenses, visas, immunizations are paid through the AMA Volunteer Physicians for Vietnam, in addition to a $50,000 all-risk insurance policy.

Address: AMA Volunteer Physicians for Vietnam
American Medical Association
535 North Dearborn Street
Chicago, Illinois 60610

Values

The Arab was telling of the time he had lost his way in the desert. Just as he was about to abandon hope and let his hunger overcome him, he found a bag of pearls. "I shall never forget," he said, "the relish and delight I felt supposing the contents of the bag to be dried wheat, nor the bitterness and despair I suffered in discovering that the bag contained nothing but pearls."*

*Red Barrel

Vision

A man once found a shiny new dime in the road. From then on his mind was focused on small things and he never lifted his eyes from the ground while walking. At the end of forty years, he accumulated 34,947 buttons, 53,712 pins, 11 pennies, a bent back and a bad disposition. He lost the glories of the light, the smiles of friends, the beauties of nature, and the opportunity to serve his fellow-men and spread happiness*

*Alexander Co-operator.

117th Annual Meeting
Minnesota State Medical Association

Duluth, Minnesota

May 18, 19, 20, 1970

"IN DEPTH" Scientific Sessions, Workshops, Noon Luncheons, Scientific and Technical Exhibits, Golf & Bridge Tournaments, Annual Banquet—there will be so much to see and do at the 117th Annual Meeting May 18, 19 and 20 in the new Duluth Civic Auditorium.

The calendar of social events is full, and includes the Annual Golf Tournament Sunday, May 17. Tee off time is 10:00 A.M. at the Northland Country Club in Duluth. The Bridge Tournament is set for 7:30 P.M. in the Ballroom of Hotel Duluth. All bridge players—physicians, their wives and guests—are invited to participate.

The dinner for Delegates and Councilors and their wives will be served at 6:00 P.M. in the Moorish Room, Hotel Duluth.

The Annual Banquet is scheduled for Monday, May 18, at 7:00 P.M. in the Ballroom, Hotel Duluth.

The President's Reception will precede the Banquet at 6:00 P.M. in the Arrowhead Room, Hotel Duluth.

The Minnesota Chapter of the American Academy of Pediatrics will have its luncheon and meeting at the Kitchi Gammi Club Monday, May 18, at 12:15 P.M. The speaker for the Academy luncheon will be Mr. James Fish; his topic will be "Migrants, Inc."

The Minnesota Society of Clinical Pathologists will hold its annual meeting Tuesday, May 19, beginning at 9:30 A.M. in the Duluth Auditorium. Their program will include the following: Morning Session, Duluth Civic Auditorium, 9:30 A.M. to 12:00 noon, "Chemical vs. Clinical Pathology: Or What the Clinician Wants from the Pathologist," Richard L. Reece, Minneapolis; "The One Best Test of Thyroid Function," Donald J. Nollet, Hibbing; "Should You Take Your Laboratory Results Lying Down? The Effect of Posture on Normal Values," Seymour Handler, Minneapolis; 12:15 Luncheon, Kitchi Gammi Club; Afternoon Session, Duluth Civic Auditorium, 2:00 P.M. to 5:00 P.M., "Is Lipoprotein Electrophoresis Really Necessary?" Ralph D. Ellefson, Ph.D., Rochester; "pO_2?" Martin A. Segal, Minneapolis; "The Pathologist and the Pill," Donald M. Larson, Duluth.

Many of the nearly 50 scientific and nonscientific committees of the Association have scheduled 7:30 A.M. committee breakfasts in conjunction with the meeting. Physicians are invited to attend their respective committee breakfasts Monday through Wednesday.

On the business side of the program, the House of Delegates will convene Sunday, May 17, at 2:00 P.M., in the Ballroom, Hotel Duluth. Registration of Delegates will begin at 1:30 P.M. The second session of the House will be called to order Tuesday, May 19, at 7:00 P.M.

The following reference committees will meet Sunday at 7:30 P.M. following the dinner for Delegates and Councilors: Medical Practice, Room 418; Medical Organization, Room 419; Professional Relations, Norse Room; Medical Economics, Arrowhead Room; Officers and Councilors, Italian Room; and Resolutions, Parlor B, all at Hotel Duluth. Physician attendance at reference committee hearings is encouraged.

Scientific Sessions will begin Monday, May 18, at 9:00 A.M. in the Duluth Auditorium with an "IN DEPTH" presentation of "Disorders of Calcium Metabolism." Additional Scientific Sessions, Workshops and Annual Meeting events are listed in the following Annual Meeting timetable and in the official Annual Meeting program mailed to all physicians:

MONDAY, MAY 18

A.M.	Visit scientific and technical exhibits "DISORDERS OF CALCIUM METABOLISM" Moderator—Ralph S. Goldsmith, Rochester
9:00	WHAT'S NEW AND NEWS IN CALCIUM METABOLISM Claude D. Arnaud, Rochester
9:30	OSTEOPOROSIS Byron L. Riggs, Rochester
10:00	INTERMISSION—Visit scientific and technical exhibits
10:30	CALCIUM UROLITHIASIS Lynwood H. Smith, Rochester
11:00	HYPERCALCEMIA Ralph S. Goldsmith, Rochester
11:30	ROUND TABLE DISCUSSION—QUESTIONS FROM AUDIENCE—Claude D. Arnaud Byron L. Riggs, Lynwood H. Smith, Ralph S. Goldsmith, Rochester
12:30 P.M.	LUNCHEON Consulting Psychologist Dr. James F. Martin, Minneapolis "COMMUNICATION": Physician-Patient "WHO NEEDS IT?!" Physician-Spouse
1:30 P.M.	Visit scientific and technical exhibits
2:00 P.M. to 3:00 P.M.	WORKSHOPS
3:00 P.M. to 3:45 P.M.	Visit scientific and technical exhibits
3:45 P.M. to 4:45 P.M.	WORKSHOPS (repeated)
6:00 P.M.	PRESIDENT'S RECEPTION
7:00 P.M.	ANNUAL BANQUET Presentations and Entertainment Dancing and Late Evening Buffet

TUESDAY, MAY 19

A.M.	Visit scientific and technical exhibits "WHAT'S NEW IN HEART DISEASE" John G. Fee, Presiding (Morning program arranged in cooperation with the Minnesota Heart Association)
9:00 A.M.	OFFICE DIAGNOSIS OF CONGENITAL HEART DISEASE Russell V. Lucas, Minneapolis
9:30 A.M.	CORONARY ARTERIOGRAPHY, DIAGNOSIS AND TREATMENT George G. Rowe, Madison, Wisconsin
10:00 A.M.	DIAGNOSIS AND TREATMENT OF PULMONARY EMBOLIC DISEASE Arthur A. Sasahara, West Roxbury, Massachusetts
10:30 A.M. to 11:00 A.M.	Visit scientific and technical exhibits
11:00 A.M.	REHABILITATION AFTER MYOCARDIAL INFARCTION Herbert A. Schoening, Minneapolis
11:25 A.M.	MEDICAL TREATMENT OF ARRHYTHMIAS T. Paul B. O'Donovan, Rochester
12:30 P.M.	LUNCHEON Richard V. Ebert, Minneapolis "NEWER APPROACHES TO MEDICAL EDUCATION"
1:30 P.M.	Visit scientific and technical exhibits
2:00 P.M. to 3:00 P.M.	WORKSHOPS
3:00 P.M. to 3:45 P.M.	Visit scientific and technical exhibits
3:45 P.M. to 4:45 P.M.	WORKSHOPS (repeated)

WEDNESDAY, MAY 20

A.M.	Visit scientific and technical exhibits "WHAT'S NEW IN HEART DISEASE" (Continued) James N. Karnegis, Presiding (Program arranged in cooperation with the Minnesota Heart Association)
9:00 A.M.	DIAGNOSIS AND TREATMENT OF COMMON HYPERLIPIDEMIAS Kenneth G. Berge, Rochester
9:30 A.M.	MODERN TREATMENT OF HEART FAILURE Yang Wang, Minneapolis
10:00 A.M.	DIAGNOSIS AND CURRENT TREATMENT OF STROKE Joseph A. Resch, Minneapolis
10:30 A.M. to 11:00 A.M.	Visit scientific and technical exhibits
11:00 A.M.	PERICARDITIS Howard B. Burchell, Minneapolis
11:30 A.M.	TREATMENT OF BACTERIAL ENDOCARDITIS Wesley W. Spink, Minneapolis

Identical workshop sessions will be held on Monday and Tuesday, May 18 and 19, at 2:00-3:00 P.M. and 3:45-4:45 P.M., as follows:

MONDAY, MAY 18

Massively Injured Patient	J. F. Perry, Jr., Moderator; J. Cleary, J. Fuller, C. R. Hitchcock
Radiological Workshop	A. I. Balmer
Exercise for Coronary Disease—When, Where & How	C. R. Jorgensen
Reading & Learning Disorders in Children	J. F. Mellinger
Contraceptives	W. B. Stromme, Moderator; B. F. P. Williams, T. C. Carrier, G. E. Holt
Antibiotics	A. C. Kind
Suction Completion of Abortion	J. H. Pratt, Jr.

Office Neurology—Diagnosis & Treatment	L. A. Farber
TUESDAY, MAY 19	
Facial Injuries	J. A. Hilger
Unconscious Patient	J. R. Brown
Office ENT	M. M. Paparella
Erythroblastosis	M. J. B. Strickland, H. F. Polesky, E. Banner
Immunizations	H. H. Reed, J. E. Kwako
Arrhythmias, Blocks and Pacemakers	N. Tuna, G. T. Gau
Treatment of Angina Pectoris	G. G. Rowe, G. K. Danielson
Infants with Heart Disease	J. H. Moller, A. R. Castaneda

Physicians pre-registration is suggested to save time. By pre-registering physicians can have their badge waiting at the Advance Registration Desk in the Duluth Auditorium. Attendance at workshop sessions is limited, and physicians are urged to select workshop topics and times and return this information on pre-registration materials enclosed with special mailings, including the monthly Newspage and the official Annual Meeting Program.

The scientific program is acceptable for 13 prescribed hours by the American Academy of General Practice.

CONSTRICTIVE PERICARDITIS

Of 21 patients operated on for constrictive pericarditis, four died postoperatively but 13 are known to be working full time.

The condition may be caused by tuberculosis or viral infection. In the latter case it is called nonspecific. The Coxsackie B_5 virus has sometimes been found in the feces of patients.

In the tuberculous group the average duration of illness before operation is three years, compared with ten months in the viral group. The tuberculous cases are sparsely scattered over many years whereas the nonspecific cases appear in epidemic crops.

In the tuberculous cases the pericardium is greatly thickened, to about 1 cm., with areas of calcification or necrosis; in the virus group it is smooth and less thickened. The onset is gradual in the tuberculous cases and acute in the virus group. The tuberculous cases often show a tendency to invade the myocardium, which is rare in the virus group.

Early operation is essential in the viral group. Tuberculous pericarditis does not respond well to pericardiectomy during the acute phase. If it is diagnosed in this phase, operation should be preceded by several months of chemotherapy. Both ventricles must be completely freed of the constrictive pericardium for a good functional result. A left thoracotomy gives the best exposure for this purpose.

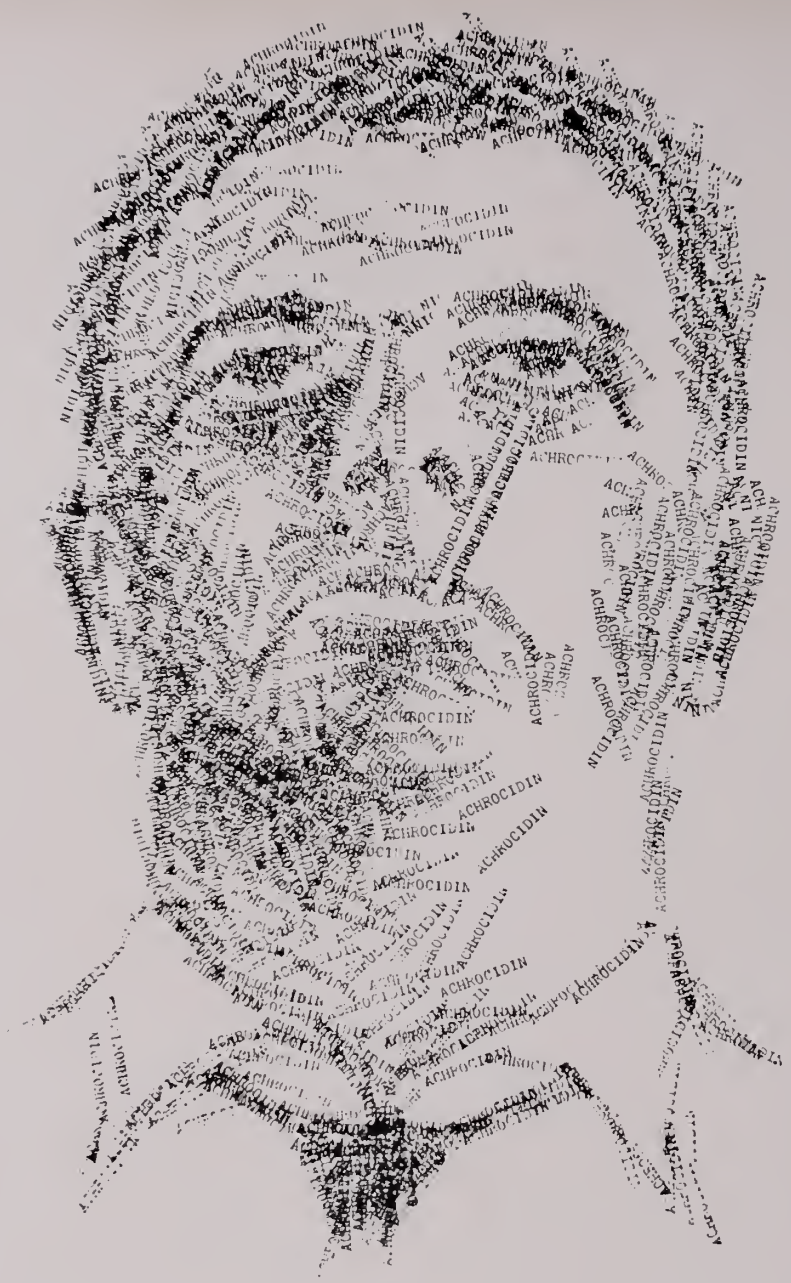
Courtesy of World-Wide Abstracts

Robertson, R., and Arnold, C.: Circulation 26:4:1:525.

Trust

We used to trust in God. I think it was in 1863 that some genius suggested that "In God we trust" be put upon the gold and silver coins which circulated among the rich. They didn't put it upon the nickels and coppers because they didn't think the poor folks had any trust in God.

—Mark Twain



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ACHROCIDIN Tetracycline HCl—Antihistamine—Analgesic Compound Tablets and Syrup are recommended for the treatme of tetracycline-sensitive bacterial infection which may complicate vasomotor rhinitis, sinusitis and other allergic diseases of t upper respiratory tract, and for the concomitant symptomatic relief of headache and nasal congestion. For children and elde patients you may prefer caffeine-free ACHROCIDIN Syrup. Each 5 cc contains: ACHROMYCIN Tetracycline equivalent Tetracycline HCl 125 mg.; Phenacetin 120 mg.; Salicylamide 150 mg.; Ascorbic Acid (C) 25 mg.; Pyrilamine Maleate 15 m.

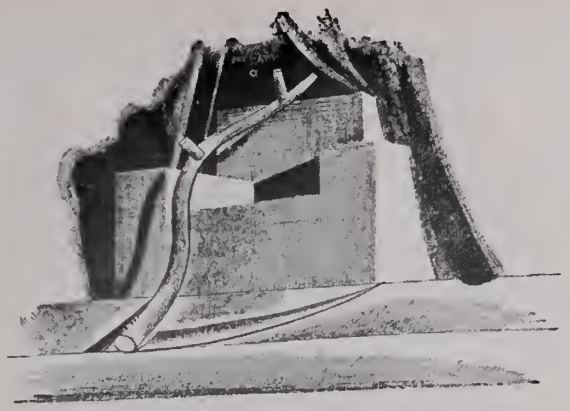
Contraindications: Hypersensitivity to any component.

Warning: In renal impairment, since liver toxicity is possible, lower doses are indicated; during prolonged therapy consider serum level determinations. Photodynamic reaction to sunlight may occur in hypersensitive persons. Photosensitive individuals should avoid exposure; discontinue treatment if skin discomfort occurs.

Precautions: Drowsiness, anorexia, slight gastric distress can occur. In excessive drowsiness, consider longer dosage intervals. Persons on full dosage should not operate vehicles. Nonsusceptible organisms may overgrow; treat superinfection appropriately. Treat beta-hemolytic streptococcal infections at least 10 days to help prevent rheumatic fever or acute glomerulonephritis. Tetracycline may form a stable calcium complex in bone-forming tissue and may cause dental staining during tooth development (last half of pregnancy, neonatal period, infancy, early childhood).

Adverse Reactions: *Gastrointestinal*—anorexia, nausea, vomiting, diarrhea, stomatitis, glossitis, enterocolitis, pruritus ani. *Skin*—maculopapular and erythematous rashes; exfoliat dermatitis; photosensitivity; onycholysis, r discoloration. *Kidney*—dose-related rise BUN. *Hypersensitivity reactions*—urticar angioneurotic edema, anaphylaxis. *Intracra* —bulging fontanels in young infants. *Teet* yellow-brown staining; enamel hypoplas *Blood*—anemia, thrombocytopenic purpu neutropenia, eosinophilia. *Liver*—cholestasis high dosage.

Upon adverse reaction, stop medication a treat appropriately.



In Memoriam

It is an old belief
That on some solemn shore,
Beyond the sphere of grief,
Dear friends shall meet once more
J. G. Lockhart

JOHN S. MILTON, M.D.

Dr. John Swanson Milton, 69, Minneapolis surgeon, died March 15. A member of The Swedish Hospital medical staff for thirty-eight years, Dr. Milton had served as Chief of Staff of the hospital in 1950 and had been a member of the hospital's board of trustees for 15 years and chairman of the Nursing School Committee.

A graduate of Augustana College, Rock Island, Illinois, Dr. Milton received his medical degree from the University of Minnesota and did postgraduate work in Edinburgh, Scotland; Stockholm, Sweden; and Cook County Hospital, Chicago.

He was a member of the American Medical Association, the Minnesota State Medical Association and the Hennepin County Medical Society.

Dr. Milton is survived by his wife and daughter.

HAROLD A. KAPLAN, M.D.

Dr. Harold A. Kaplan, 51, Minneapolis internist, died March 4. Born in Minneapolis, Dr. Kaplan obtained his medical degree from the University of Minnesota.

He was a diplomate in internal medicine and a member of the American Medical Association, the Minnesota State Medical Association and the Hennepin County Medical Society.

He is survived by his wife and two daughters.

RICHARD H. LINDQUIST, M.D.

Dr. Richard H. Lindquist, 74, Minneapolis physician for 44 years, died March 6. He was a graduate of the University of Minnesota and taught electrocardiology there. Also he was an instructor of nursing at Swedish Hospital and later chief of electrocardiology and chief of staff.

Dr. Lindquist was a member of the American Medical Association and the Hennepin County Medical Society and was a Life Member of the Minnesota State Medical Association.

He is survived by his wife, two daughters and a son.

EDWIN R. DUFF, M.D.

Dr. Edwin R. Duff, 70, Minneapolis physician, died February 13. He was born in Dazey, North Dakota, and received his medical degree from Loyola University in Chicago.

Dr. Duff was a member of the American Medical Association, the Minnesota State Medical Association and the Hennepin County Medical Society.

He is survived by his wife and four sons.

FREDERICK A. FIGI, M.D.

Dr. Frederick A. Figi, 77, nationally-known plastic surgeon and doctor emeritus of the Mayo Clinic, died March 21. He was a native of Sutton, Nebraska, attended Deane College, received a medical degree from the University of Nebraska in 1918 and became a fellow in the Mayo Clinic Graduate School in 1918.

Dr. Figi was a member of the American Medical Association and the Zumbro Valley Medical Society and a 50 Club and Associate Member of the Minnesota State Medical Association.

He is survived by his wife and two daughters.

STANLEY W. ROBERTS, M.D.

Dr. Stanley W. Roberts, 64, Minneapolis surgeon, died March 19. His medical degree was obtained from the Universities of South Dakota and Nebraska.

He was a member of the American Medical Association, the Minnesota State Medical Association and the Hennepin County Medical Society.

Dr. Roberts is survived by his wife and two daughters.

in active stages of moderate to severe rheumatoid arthritis

What more can you

after you've tried



rheumatoid spondylitis, and osteoarthritis of the hip

do for these patients?

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REVISED PRESCRIBING INFORMATION

IMPORTANT NOTE: INDOCIN (Indomethacin, MSD) cannot be considered a simple analgesic and should not be used in conditions other than those recommended under Indications. The drug should not be prescribed for children because safe conditions for use have not been established.

General Adverse Effects: Because of the high potency of the drug and the variability of its potential to cause adverse reactions, the following are strongly recommended: 1) the lowest possible effective dose for the individual patient should be prescribed. Increased dosage tends to increase adverse effects, particularly in doses over 150-200 mg/day, without corresponding clinical benefits; and 2) careful instructions to, and observations of, the individual patients are essential to the prevention of serious and irreversible, including fatal, adverse reactions, especially in the aging patient.

Indications: Symptomatic relief of adult rheumatoid and degenerative joint disease unresponsive to adequate trial of salicylates and other measures of established value, such as appropriate rest. Has been found effective in active stages of: 1) moderate to severe rheumatoid arthritis including acute flares of chronic disease, 2) moderate to severe rheumatoid (ankylosing) spondylitis, and 3) moderate to severe degenerative joint disease of the hip (osteoarthritis of the hip). Has been found effective in relieving pain and reducing fever, swelling, and tenderness in acute gouty arthritis in selected patients. May enable reduction of steroid dosage in patients receiving steroids for the more severe forms of rheumatoid arthritis; in such instances the steroid dosage should be reduced slowly and the patients followed very closely for any possible adverse effects.

Contraindications: Children 14 years of age and under; pregnant women and nursing mothers; active gastrointestinal lesions or history of recurrent gastrointestinal lesions; allergy to aspirin and indomethacin.

Warnings: *Gastrointestinal Effects:* Because of the occurrence and, at times, severity of gastrointestinal reactions, be continuously alert for any sign or symptom signaling a possible gastrointestinal reaction. The risks of continuing therapy with INDOCIN in the face of such symptoms must be weighed against the possible benefits to the individual patient. Gastrointestinal effects may be reduced by giving the drug immediately after meals, with food, or with antacids. Use greater care in aging patients.
Ocular Effects: Corneal deposits and retinal disturbances, including those of the macula, have been observed in some patients on prolonged therapy. Discontinue therapy if such changes are observed. Ophthalmologic examination at periodic intervals is desirable in patients on prolonged therapy.
Central Nervous System Effects: INDOCIN (Indomethacin, MSD) may aggravate psychiatric disturbances, epilepsy, and parkinsonism, and should be used with considerable caution in patients with these conditions. If severe CNS reactions develop, discontinue the drug.

Precautions: Blurred vision may be a significant symptom that warrants a thorough ophthalmologic examination. Patients should be cautioned about engaging in activities requiring mental alertness and motor coordination, as driving a car. Headache which persists despite dosage reduction requires complete cessation of the drug. May mask the usual signs and symptoms of infection; therefore, the physician must be continually on the alert for this and should use the drug with extra care in the presence of existing controlled infection. After the acute phase of the disease is under control, an attempt to reduce the daily dose should be made repeatedly until the patient is off entirely.

Adverse Reactions: *Gastrointestinal Reactions:* Single or multiple ulcerations of the esophagus, stomach, duodenum, or small intestine, including perforation and hemorrhage, with fatalities in some instances; gastrointestinal bleeding without obvious ulcer formation; perforation of preexisting sigmoid lesions (diverticulum, carcinoma, etc.); rarely, increased abdominal pain in ulcerative colitis patients or development of ulcerative colitis and regional ileitis; gastritis, which may persist after the cessation of the drug; nausea, vomiting, anorexia, epigastric distress, abdominal pain, and diarrhea.
Eye Reactions: Corneal deposits and retinal disturbances, including those of the macula, have been observed on prolonged therapy; blurring of vision.
Hepatic Reactions: Rarely, toxic hepatitis and jaundice, including some fatal cases.
Hematologic Reactions: Aplastic anemia, hemolytic anemia, bone marrow depression, agranulocytosis, leukopenia, and thrombocytopenic purpura. Since some patients manifest anemia secondary to obvious or occult gastrointestinal bleeding, appropriate blood determinations are recommended.
Hypersensitivity Reactions: Acute respiratory distress, including dyspnea and asthma; angiitis; pruritus; urticaria; angioedema; skin rashes.
Ear Reactions: Hearing disturbances, deafness, tinnitus.
Central Nervous System Reactions: Psychotic episodes, depersonalization, depression, coma, convulsions, peripheral neuropathy, drowsiness, mental confusion, lightheadedness, dizziness, headache.
Cardiovascular-Renal Reactions: Edema, elevation of blood pressure, hematuria.
Dermatologic Reactions: Loss of hair, erythema nodosum.
Miscellaneous: Rarely, vaginal bleeding, hyperglycemia, glycosuria, ulcerative stomatitis, and epistaxis.

Supplied: Capsules containing 25 mg indomethacin each, in bottles of 100 and 1000; capsules containing 50 mg indomethacin each, in bottles of 100.

For more detailed information, consult your Merck Sharp & Dohme representative or see the package circular.

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Continued from page 556.

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EXCELLENT FIVE-YEAR-OLD, all-electric hydraulic Ritter table, $1,200. Call 612-473-7303, Wayzata.

TWO ASSOCIATES needed to join 39-year-old in the practice of Family Medicine. Medical clinic adjacent to 27-bed hospital; both built in 1960; hospital recently acquired 3 year OCAH accreditation. Community 40 miles west of Minneapolis. If interested, contact Anton J. Stifter, M.D., 612-485-2622; home phone 485-2230; call collect.

The Test of Tact

In my college psychology textbook I include a "Test of Tact." From page 788 comes Problem #22:

A butler accidentally opens the bathroom door while the lady of the house is bathing. He should say:

(a) "Oh, excuse me, Madam. I didn't know you were in here."
(b) "You should have locked the door."
(c) "Oh, excuse me, Sir."

When that ran in my syndicated newspaper quiz column called "Test Your Horse Sense," the telephones were jammed at the Chicago Tribune and New York News, for hundreds of chemists, accountants, and introvertive clergymen phoned to protest. They thought I had made an error in listing the answer at (c) as correct, for they argued, "Dr. Crane, there was no man in the tub!" But this was a test of tact!*

*Dr. George Crane: The Quotable Dr. Crane, 1968.

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According to Goodyear Tire & Rubber Co., heavy-footed motorists can grind as much as 5,000 miles of tread life off a set of tires in a single evening of jackrabbit starts, screeching turns and panic stops. That's more mileage than the average driver puts on his car in six months.

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Wild Hollyhocks" — *Thomas J. Kinsella, M.D.*

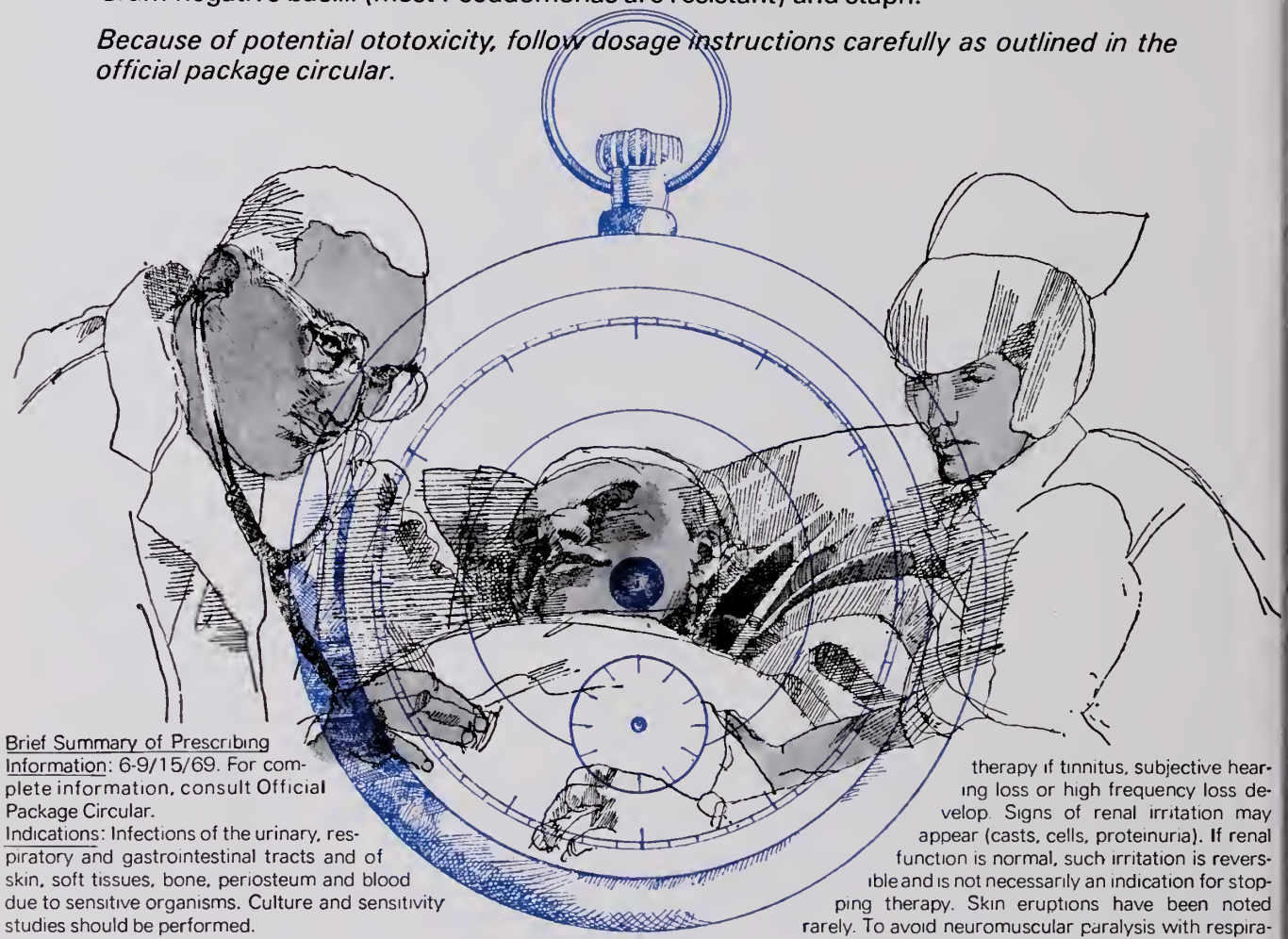
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A valuable hospital antibiotic —when there is no time

in severe systemic infections—postoperative bacteremia, Gram-negative/staph pneumonias or neonatal sepsis—Kantrex® (kanamycin sulfate) is often indicated before results of customary sensitivity tests can be reported. Clinical response is often seen within 24-48 hours in susceptible infections, with remission soon after.

10 years of experience confirm the continuing effectiveness of Kantrex® against many Gram-negative bacilli (most Pseudomonas are resistant) and staph.

Because of potential ototoxicity, follow dosage instructions carefully as outlined in the official package circular.



Brief Summary of Prescribing Information: 6-9/15/69. For complete information, consult Official Package Circular.

Indications: Infections of the urinary, respiratory and gastrointestinal tracts and of skin, soft tissues, bone, periosteum and blood due to sensitive organisms. Culture and sensitivity studies should be performed.

Contraindications: A history of hypersensitivity to the drug. Prior auditory damage by kanamycin or other agents may be a contraindication if effective alternative therapy is available.

Warnings: Since the drug is excreted almost entirely by glomerular filtration, renal malfunction can cause abnormally high serum levels of kanamycin which may prove ototoxic. Assess renal function periodically, both before and during therapy. Renal dysfunction or pre-renal azotemia sharply increase the risk of ototoxicity and permanent deafness. In such cases decrease the size and frequency of doses. Discontinue kanamycin and check hearing if azotemia increases. In older patients and patients receiving a total dose in excess of 15 Grams, watch carefully for signs of ototoxicity.

Precautions: If mycotic or bacterial superinfection occurs, discontinue kanamycin and initiate appropriate therapy. Cumulative ototoxic effects may be produced by concurrent or consecutive use of other ototoxic drugs. High doses may cause irritation at injection sites. The drug *should not* be physically mixed with other antimicrobials.

Adverse Reactions: Severe irreversible hearing loss may occur. Stop therapy if tinnitus, subjective hearing loss or high frequency loss develop. Signs of renal irritation may appear (casts, cells, proteinuria). If renal function is normal, such irritation is reversible and is not necessarily an indication for stopping therapy. Skin eruptions have been noted rarely. To avoid neuromuscular paralysis with respiratory depression, postpone intraperitoneal instillation in postoperative patients until recovery from anesthesia and muscle relaxants is complete.

Dosage and Administration: The usual dose is 7.5 mg./Kg./12 hours I.M. The average adult dose is 1 Gram daily and should not exceed 1.5 Gram even in the heaviest patients. Uncomplicated infections due to sensitive organisms should respond in 24 to 48 hours. If no response occurs in 5 days, stop therapy and recheck the bacterial sensitivities. Hydrate patients well to minimize renal irritation. Inject deeply into the upper outer quadrant of the gluteal muscle. Discard partially used vials after 48 hours.

Supplied: Rubber capped vials as a ready-to-use sterile aqueous solution in two concentrations: 0.5 Gm. in 2 ml. 1.0 Gm. in 3 ml.

Also available—Pediatric Injection 75 mg. in 2 ml.

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TABLETS & GRANULES

■ **to help restore and stabilize the intestinal flora**

■ **for fever blisters and canker sores of herpetic origin**

Lactinex contains both *Lactobacillus acidophilus* and *L. bulgaricus* in a standardized viable culture, with the naturally occurring metabolic products produced by these organisms.

Lactinex has been shown to be useful in the treatment of gastrointestinal disturbances, and for relieving the painful oral lesions of fever blisters and canker sores of herpetic origin.[1,2,3,4,5,6,7,8]

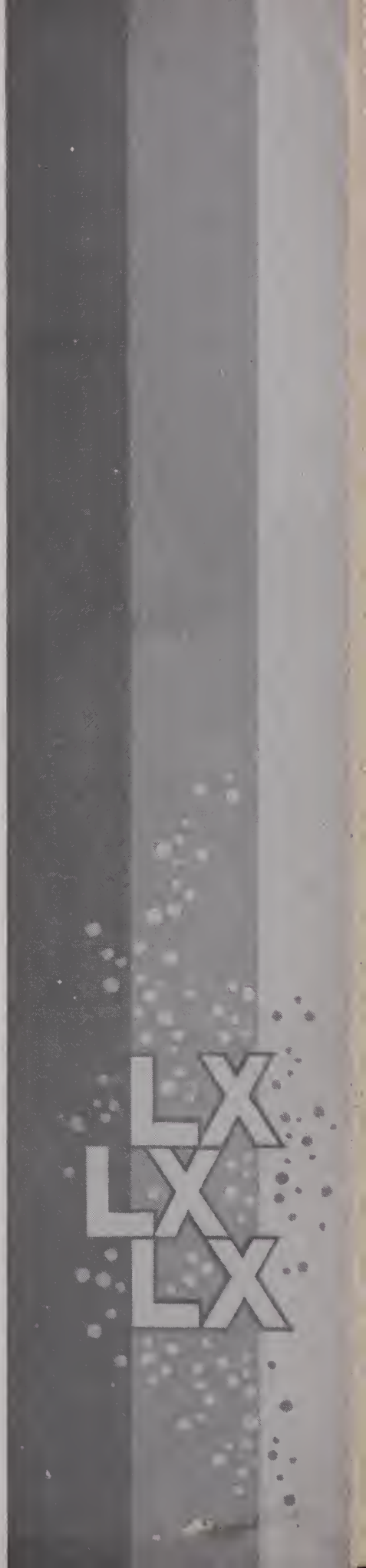
No untoward side effects have been reported to date.

Literature on indications and dosage available on request.

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References:
(1) Siver, R. H.: CMD, *21*:109, September 1954. (2) Frykman, H. H.: Minn. Med., *38*:19-27, January 1955. (3) McGivney, J.: Tex. State Jour. Med., *51*:16-18, January 1955. (4) Quehl, T. M.: Jour. of Florida Acad. Gen. Prac., *15*:15-16, October 1965. (5) Weekes, D. J.: N.Y. State Jour. Med., *58*:2672-2673, August 1958. (6) Weekes, D. J.: EENT Digest, *25*:47-59, December 1963. (7) Abbott, P. L.: Jour. Oral Surg., Anes., & Hosp. Dental Serv., 310-312, July 1961. (8) Rapoport, L. and Levine, W. I.: Oral Surg., Oral Med. & Oral Path., *20*:591-593, November 1965.



A urinary tract infection was eliminated last week

Intestinal monilial overgrowth has appeared this week

For women who are diabetic or debilitated, oral antibiotic therapy often sets the stage for monilial overgrowth in the intestine.

When you anticipate such a problem, take action with DECLOSTATIN 300. It combines the broad-spectrum potency of demethylchlortetracycline with the antifungal effectiveness of nystatin—it helps avoid monilial take-over. Experience has shown DECLOSTATIN to be highly useful for many women patients; individual culture studies will show exactly where this usefulness may best be applied.

It doesn't let monilia begin where bacteria end. Declostatin® 300

Demethylchlortetracycline HCl 300 mg and
Nystatin 500,000 units Capsule-Shaped Tablets Lederle

Effectiveness: Because its antibacterial component is DECLOMYCIN ® Demethylchlortetracycline, DECLOSTATIN should be equally or more effective therapeutically than other tetracyclines in infections caused by tetracycline-sensitive organisms. The antifungal component, nystatin, protects against superinfection by antibiotic-resistant fungal overgrowth (particularly monilia) in the intestinal tract.

Contraindication: History of hypersensitivity to demethylchlortetracycline or nystatin.

Warning: In renal impairment, usual doses may lead to excessive accumulation and liver toxicity. Under such conditions, lower than usual doses are indicated and, if therapy is prolonged, serum level determinations may be advisable. A photodynamic reaction to natural or artificial sunlight has been observed. Small amounts of drug and short exposure may produce an exaggerated sunburn reaction which may range from erythema to severe skin manifestations. In a smaller proportion, photoallergic reactions have been reported. Patients should avoid direct exposure to sunlight and discontinue drug at the first evidence of skin discomfort. Necessary subsequent courses of treatment with tetracyclines should be carefully observed.

Precautions: Overgrowth of nonsusceptible organisms may occur. Constant observation is essential. If new infections appear, appropriate measures should be taken. In infants, increased intracranial pressure with bulging fontanels has been observed. All signs and symptoms have disappeared rapidly upon cessation of treatment.

Side Effects: Gastrointestinal system—anorexia, nausea, vomiting, diarrhea, stomatitis, glossitis, enterocolitis, pruritus ani. Skin—maculopapular and erythematous rashes; a rare case of exfoliative dermatitis has been reported. Photosensitivity; onycholysis and discoloration of the nails (rare). Kidney—rise in BUN, apparently dose-related. Transient, reversible, nephrogenic diabetes insipidus with excessive thirst and polyuria (rare). Hypersensitivity reactions—urticaria, angioneurotic edema, anaphylaxis. Teeth—dental staining (yellow-brown) in children of mothers given this drug during the latter half of pregnancy, and in children given the drug during the neonatal period, infancy and early childhood. Enamel hypoplasia has been seen in a few children. If adverse reaction or idiosyncrasy occurs, discontinue medication and institute appropriate therapy. Demethylchlortetracycline may form a stable calcium complex in any bone-forming tissue with no serious harmful effects reported thus far in humans.

Average Adult Daily Dosage: One tablet b.i.d. Should be given 1 hour before or 2 hours after meals, since absorption is impaired by the concomitant administration of high calcium content drugs, foods and some dairy products. Treatment of streptococcal infections should continue for 10 days, even though symptoms have subsided.

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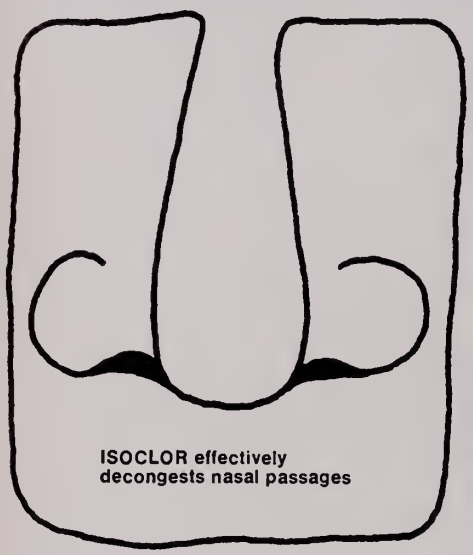
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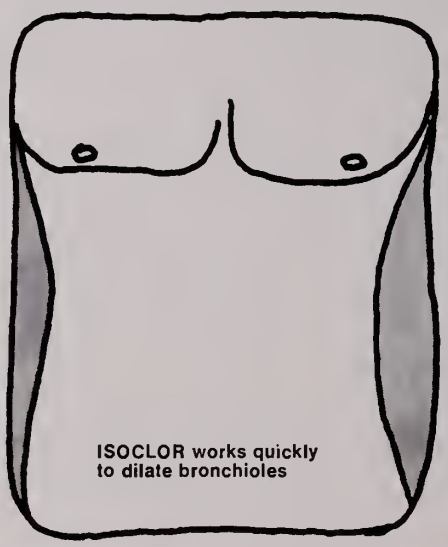
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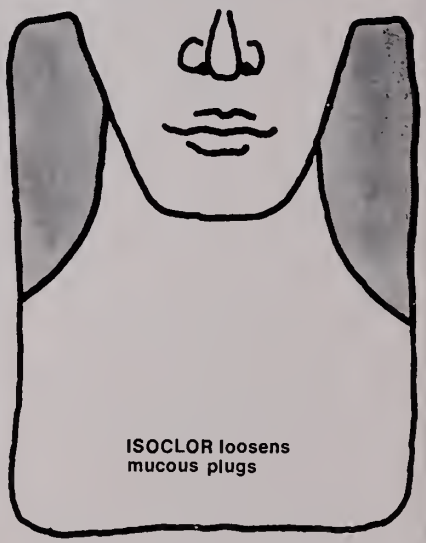
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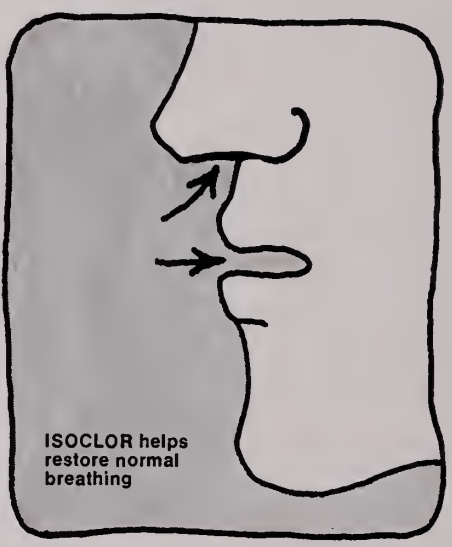
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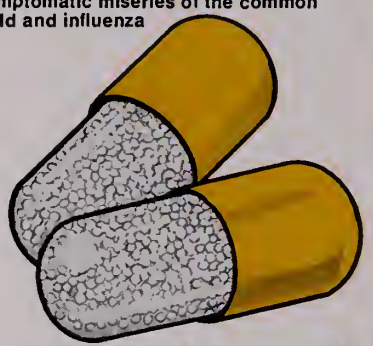


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ISOCLOR helps restore normal breathing

ISOCLOR promptly and effectively combats symptomatic miseries of the common cold and influenza



ISOCLOR helps patients face the cold facts

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Isoclor provides quick, long lasting relief of respiratory congestion and discomfort brought on by common colds, influenza, and allergies. Isoclor contains chlorpheniramine maleate — one of the most potent and safest antihistamines. And pseudoephedrine HCl — a decongestant bronchodilator providing effective and long lasting relief for the entire respiratory tract. Both work to extend the range of relief.

COMPOSITION: Each tablet or 2 teaspoonfuls of liquid contains:
Chlorpheniramine Maleate.....4 mg.
Pseudoephedrine HCl.....25 mg.

Each ISOCLOR Timesule contains:

Chlorpheniramine Maleate.....10 mg.
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In a special pellet form providing both prompt and sustained effect.

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CONTRAINDICATIONS: Sensitivity to antihistamines or sympathomimetic agents. Severe hypertension or severe cardiac disease.

PRECAUTIONS: Use with caution in patients suffering with hyperthyroidism. Patients susceptible to the soporific effects of chlorpheniramine should be warned against driving or operating machinery should drowsiness occur.

CAUTION: Federal law prohibits dispensing without prescription.

SUPPLIED: Tablets: Bottles of 100 and 1000. Liquid: 4 oz. bottles, pints, and gallons; Timesules: Bottles of 50, 250, and 1000.

DOSAGE AND ADMINISTRATION:	Tablets	Liquid	Timesule
Adults:	1 q. 4 h.	2 tsp. q. 3-4 h.	1 q. 12 h.
Children 6-12 years:		1 tsp. q. 3-4 h.	
40-50 pounds:		¾-1 tsp. q. 3-4 h.	
30-40 pounds:		½-¾ tsp. q. 3-4 h.	
20-30 pounds:		¼-½ tsp. q. 3-4 h.	
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See the President's Letter, Page 603.

The girth control pill



Tepanil® Ten-tab®

(continuous release form)

(diethylpropion hydrochloride)

works on the appetite not on the 'nerves'

When girth gets out of control, TEPANIL can provide sound support for the weight control program you recommend. TEPANIL reduces the appetite—patients enjoy food but eat less. Weight loss is significant—gradual—yet there is a relatively low incidence of CNS stimulation.

Contraindications: Concurrently with MAO inhibitors, in patients hypersensitive to this drug; in emotionally unstable patients susceptible to drug abuse.

Warning: Although generally safer than the amphetamines, use with great caution in patients with severe hypertension or severe cardiovascular disease. Do not use during first trimester of pregnancy unless potential benefits outweigh potential risks.

Adverse Reactions: Rarely severe enough to require discontinuation of therapy, unpleasant symptoms with diethylpropion hydrochloride have been reported to occur in relatively low incidence. As is characteristic of sympathomimetic agents, it may occasionally cause CNS effects such as insomnia, nervousness, dizziness, anxiety, and jitteriness. In contrast, CNS depression has been reported. In a few epileptics an increase in convulsive episodes has been reported. Sympathomimetic cardiovascular effects reported include ones such as tachycardia, precordial pain, arrhythmia, palpitation, and increased blood pressure. One published report described T-wave changes in the ECG of a healthy young male after ingestion of diethylpropion hydrochloride; this was an isolated experience, which has not been reported by others. Allergic phenomena reported include such conditions as rash, urticaria, ecchymosis, and erythema. Gastrointestinal effects such as diarrhea, constipation, nausea, vomiting, and abdominal discomfort have been reported. Specific reports on the hematopoietic system include two each of bone marrow depression, agranulocytosis, and leukopenia. A variety of miscellaneous adverse reactions have been reported by physicians. These include complaints such as dry mouth, headache, dyspnea, menstrual upset, hair loss, muscle pain, decreased libido, dysuria, and polyuria.

Convenience of two dosage forms: TEPANIL Ten-tab tablets: One 75 mg. tablet daily, swallowed whole, in midmorning (10 a.m.); TEPANIL: One 25 mg. tablet three times daily, one hour before meals. If desired, an additional tablet may be given in midevening to overcome night hunger. Use in children under 12 years of age is not recommended.

T-006A / 1/70 / U.S. PATENT NO. 3,001,910

THE NATIONAL DRUG COMPANY
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President's Letter

Scapegoat

In biblical times, on the Day of Atonement, Aaron, the leader of the Jews, laid the sins of the people on the head of a goat which was then led away into the wilderness to suffer and possibly die for the sins of the people. This is the origin of the word, *scapegoat*.

Members of the staff of the United States Senate Finance Committee have written and issued a strongly worded report of their study of Medicare and Medicaid in which they blame increased medical costs on the providers of services, namely, physicians and hospitals. Have they forgotten that a few short years ago this same Senate Finance Committee portrayed the physician as a villain for resisting federal legislation enacting Medicare and Medicaid on the prediction that these two agencies would prove to be too costly? And now, after 3½ short years of trial and concomitant soaring medical costs, they would lead the public to believe that it is the greedy physician who is once again the villain.

Why do not members of this supposedly august and powerful Senate Finance Committee face reality and stop trying to find a *scapegoat?* Have they forgotten the years in which hospital personnel, the intern who served his tenure without pay or at most room and board, the scrubwoman, the nurse and the orderly were the most underpaid workers in any field of endeavor? Is it not inevitable that the cost of a hospital bed would rise as these gross inequities of salary are adjusted, as inflation creeps along and as hospitals and equipment therein become more sophisticated and inevitably more expensive? Commissioner of Social Security, Robert M. Ball, candidly admits that the reason Medicare is in financial trouble is that original projections did not foresee the explosive rise of hospital rates or the increased use of hospitals on the part of the aged.

In the same news release to the press which dealt with the report I have mentioned, the staff of the Senate Finance Committee charge that five Indiana physicians received more than $25,000 in fees from services rendered under Medicaid in 1968—despite the fact that Medicaid was not put into operation in Indiana until 1970. I can well understand much of the exasperation Vice President Spiro Agnew must have felt as he castigated and challenged representatives of the news media for making snap judgments on the basis of incomplete or faulty evidence. He was severely criticized by the news media for complaining that their judgments on great and vital problems actually reposed in the hands of a few. Humorously, one newspaper went so far as to state that "Agnew should be silenced in the interest of free speech."

In contrast to what the Senate Finance Committee said and our news media published, Commissioner of Social Security Ball really said that Medicare pays about 30 million

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Carotid Endarterectomy for Stroke*

DONALD L. ERICKSON, M.D.†, DON M. LONG, M.D.†,
EDWARD L. SELJESKOG, M.D.†, SHELLEY N. CHOU, M.D.†,
LYLE A. FRENCH, M.D.†

CHIARI, IN 1905, was the first to suggest a correlation between the stroke syndrome and extracranial carotid artery occlusive disease.[6] This correlation was based upon the postmortem examination of carotid vessels. The introduction of carotid angiography by Moniz in 1927 made possible the antemortem diagnosis of this condition, but it was not until 1954 that the first successful reconstruction of a stenotic carotid vessel was reported by Eastcott, Pickering and Robb.[4,7]

The various syndromes of cerebral vascular insufficiency due to carotid artery stenosis are now well recognized, the technical aspects of surgery are well developed, and the value of operative therapy is accepted.[2,3] However, the indications for operative intervention in this disease are not clearly defined. The value of this operative procedure must, without question, be judged on the basis of clinical improvement and not simply by the demonstration of a successfully reconstructed vessel.[6] The purpose of this review is to help in the establishment of reasonable guidelines in the selection of patients for carotid artery surgery. Even though the mortality and morbidity associated with this surgical procedure are low, it is mandatory to select only patients with a reasonable chance of obtaining benefit.

Material

Included in this report are 100 consecutive patients who have undergone carotid endarterectomy or thromboendarterectomy on the Neurosurgery Service at the University of Minnesota Hospitals. Eight of these patients had bilateral carotid surgery, giving a total of 108 operative procedures. Data concerning presenting symptoms, neurological examination, angiographic abnormalities, and clinical results were compiled for each patient.

Clinical Grouping

The patients were placed in one of three groups on the basis of history and neurological findings. *Group 1* included patients with the history of transient cerebral ischemic episodes (defined as multiple stroke-like syndromes of transient nature characteristically with similar symptoms repeatedly) and a normal neurological examination. *Group 2* consisted of patients with a similar history, but with evidence of significant neurological deficit on examination. *Group 3* was composed of patients with either acute onset of significant neurological deficit or a permanent neurological deficit and no history of previous transient ischemic attacks. Table 1 shows a distribution of patients within these three groups.

TABLE 1
Clinical Response to Surgery

Number of Patients	Improved	Worsened	Unchanged	Deaths
	Transient Ischemic Attacks			
29	26	0	3	0
	90%	0%	10%	0%
Transient Ischemic Attacks With Some Neurologic Deficit				
42	24	8	4	6
	57%	19%	10%	14%
Marked Stable Neurologic Deficit Or Acute Stroke				
29	4	1	18	6
	15%	4%	60%	21%

Angiographic Grouping

A second grouping was made on the basis of angiographic findings. *Group A* consisted of patients with unilateral carotid stenosis; *Group B* patients had bilateral carotid stenosis; *Group C* patients had stenosis of one carotid artery and occlusion of the other, and *Group D* patients had one normal carotid and one occluded artery (Table 2).

The clinical results were then reviewed in order to correlate outcome with these groupings. Patients were considered improved only if they had complete or nearly complete cessation of transient ischemic episodes, or sig-

*Supported by the Morris T. Baker Fund and Cerebrovascular Training Grant.
†From Department of Neurosurgery, University of Minnesota Health Sciences Center, Minneapolis, Minnesota.

nificant improvement of a neurological deficit. They were considered worsened if the neurological deficit increased even though the transient ischemic episodes were reduced in frequency. The group designated as unchanged were those having no significant difference in symptoms on neurological examination. Death from any cause in the first postoperative month was considered as surgical mortality and morbidity.

TABLE 2
Clinical Response to Surgery

Number of Patients	Improved	Worsened	Unchanged	Deaths
	Unilateral Carotid Stenosis			
51	35	5	10	1
	69%	10%	20%	2%
	Bilateral Carotid Stenosis			
23	15	2	4	2
	65%	9%	17%	9%
	Unilateral Carotid Occlusion			
9	1	0	6	2
	11%	0%	66%	23%
	Unilateral Carotid Stenosis With Contralateral Carotid Occlusion			
17	4	0	6	7
	23%	0%	35%	42%

Angiograms were performed by direct carotid puncture or retrograde brachial injection. Anteroposterior and lateral intracranial views were always included to avoid overlooking associated intracranial pathology.

Surgery

Surgery was carried out under general anesthesia, unless there was some systemic contraindication. Endarterectomy was accomplished by arteriotomy and removal of the plaque; only rarely was a patch graft inserted. Heparin was given intravenously just prior to cross-clamping the vessel, but heparinization was not continued postoperatively. Bypass shunts were commonly used unless unilateral stenosis with spontaneous crossover from the opposite cerebral circulation was seen angiographically. It was considered imperative to avoid hypotension in the postoperative period. Patients were cautiously ambulated over a period of several days.

Results

The Clinical Group

As might be expected, patients with transient ischemic attacks and normal neurological examinations (Group 1) had the best results, with 90 per cent improvement and 0 per cent mortality. None of these patients were made worse by the operative procedure. The results in Group 2 (patients with transient ischemic attacks and some degree of neurological deficit) were still quite satisfactory with 58 per cent showing improvement. There were, however, 20 per cent who had some increase in neurological deficit and a mortality of 12 per cent. The mortality in Group 3 (patients with significant neurological deficit and no history of transient ischemic attacks) was 24 per cent, and even more striking was the fact that only 15 per cent of these patients were improved. Sixty-one per cent of this group were unchanged by the operative procedure.

The Angiographic Group

The angiographic groups also presented marked variations in the clinical results. Seventy per cent of patients with unilateral carotid stenosis (Group A) showed improvement, and there was only one death in 51 patients. Success in patients with bilateral carotid stenosis (Group B) was essentially the same, with 65 per cent improvement. There were two deaths in 22 patients in this group. In nine patients operated upon for one occluded vessel (Group C) there were two deaths. Only one patient in this group improved even though blood flow was established at the time of surgery in four patients. In the angiographically assigned groups the poorest results were in patients with one occluded and one stenotic vessel (Group D). The mortality in this group of 17 patients was 42 per cent, with only 23 per cent showing any benefit from the operative procedure.

Discussion

Certain criteria have been established through the evaluation of the patients in this series which are believed helpful in the selection of candidates for carotid endarterectomy. The discussion has been restricted to neurological and angiographic evaluations; obviously the general factors common to all surgical decisions are important, but an attempt has been made to hold them as a constant.

Best Results

The combination of transient ischemic attacks with a normal neurological examination is the most favorable circumstance; 90 per cent of these individuals obtained excellent results. Even the presence of bilateral carotid stenosis

of high degree did not seem to alter the favorable prognosis. Nearly all patients with these symptoms attributable to extracranial carotid stenosis can be successfully treated surgically.

Worst Results

Unfavorable results were most frequently obtained in patients with acute cerebral infarction or a serious neurological deficit, even though it was stable. Only 15 per cent of such patients were benefitted in this category. Five of the operative deaths occurred in patients with fresh cerebral infarcts. In this category none of our patients experienced a dramatic reversal of neurological deficit following endarterectomy. Those improved would probably have been improved without surgery.

The angiographic pattern associated with the poorest postoperative result was that of unilateral carotid occlusion and contralateral carotid stenosis. Seven of the operative deaths occurred in this group of patients. Therefore it would seem that a combination of stable neurological deficit or fresh cerebral infarct with an occluded carotid vessel or a combination of occlusion and stenosis places the patient in a very high risk group with little chance of benefit by surgery. These categories represent the extremes in terms of expected results in surgical therapy for carotid vascular disease.

The decision as to whether or not operative intervention is feasible is easily made if the patient falls into one of the extreme groups. However, approximately 40 per cent of the patients in this series did not fall into either group but presented with some aspects of each. It is the patients in this group who offer the greatest challenge to surgical judgment.

Making the Choice

Consideration of all available information is necessary to insure the proper choice of therapy. This group of patients usually presented with a history of transient ischemic attacks but, in addition, also had some degree of neurological deficit. Even slight neurological deficits may indicate that the patient has minimal cerebral circulatory reserve and, therefore, will tolerate surgery less well. Although these patients are less than ideal candidates, the presence of favorable angiographic findings enhances the chance of operative success. Twenty-four patients in this group did well, and of that number 22 had stenotic but not occluded vessels. All five deaths in this clinical group occurred in patients with one stenotic and one occluded carotid artery. It appears then that this clinically less favorable group of patients with severe neurological deficit may still benefit if only carotid stenosis exists. In patients with neurological abnormalities and completely occluded vessels a high mortality and a low success rate will likely ensue. It is always tempting to recall the isolated cases which did well under adverse conditions, but good surgical judgment must include an equally good memory for the disastrous results.

Special Circumstances

There are several problems which require special mention. The first is the patient with chronically occluded arteries. This occlusion is usually over a long segment from the bifurcation in the neck to the intracranial siphon, and it is impossible to predict that such a vessel can be opened and remain open. Some vessels which have seemingly been opened successfully reocclude in a few weeks. In this series there are no patients who demonstrated any clinical benefit from such a procedure. One must also beware of intracranial lesions which mimic the neurological symptoms and signs of vascular insufficiency. Brain tumors, subdural hematomas, and cerebral aneurysms have been found in patients with carotid bruits and angiographically demonstrated carotid artery disease. There are also many patients with a combination of severe intracranial vascular disease and extracranial carotid stenosis. These intracranial lesions will be overlooked unless adequate intracranial projections are included in every angiographic evaluation for cerebral vascular insufficiency. Another point of note relates to the patient with a bilateral severe carotid stenosis and marked mental deterioration. Several such patients have shown significant improvement in intellectual functions after restoration of carotid flow.

Etiology of Ischemic Attacks

A brief discussion of the possible mechanisms by which a carotid stenosis produces a transient ischemic attack is also relevant to the problem of patient selection. One concept

involves reduction of blood flow at the stenotic site with subsequent cerebral ischemia.[6] This concept allows one to explain transient ischemia in any portion of the brain on the basis of carotid artery stenosis since it reduces the total cerebral blood flow. One example might be where symptoms are consistent with basilar artery ischemia but the stenosis is in the carotid artery. Evidence has been presented to suggest that only a very high degree of stenosis with a cross-sectional area of two square millimeters or less will actually cause a reduction of flow in the internal carotid artery.[6] Many stenotic lesions are not of that magnitude, and yet these patients may demonstrate typical transient ischemic attacks. One must invoke some additional insult such as transient hypotension to make the reduced blood flow theory tenable.

Studies of Gunning et al. suggest that platelet thrombosis at the plaque site with subsequent microembolism may be an important factor.[5] We have demonstrated microemboli in the retinal vessels in patients with transient monocular blindness. This theory is attractive in that it does not demand a high-grade carotid stenosis nor does it depend on additional simultaneous systemic changes such as hypotension. The stream pattern of blood flow could account for emboli being carried repeatedly to the same area, thus producing repeatedly identical transient attacks. This cannot explain symptoms which occur outside the distribution of the involved vessel, however. Fresh thrombi are often found adherent to the carotid plaques at the time of surgery, lending further support to this theory. We, therefore, consider surgical intervention when the plaque appears very ragged or ulcerated even though the stenosis is low grade radiographically. This is true, of course, only if the clinical symptoms are compatible with the distribution of the involved vessel.

Other systemic factors are often contributory to the genesis of transient ischemic episodes. Hypotension, either orthostatic or drug-induced, is common. Antihypertensive therapy in patients with carotid or cerebral artery stenosis must be carried out cautiously. Anemia and cardiac arrhythmia can also contribute to transient ischemic attacks.

Summary

Careful clinical assessment in combination with adequate angiography can be used to predict anticipated outcome from carotid endarterectomy.

Patients who have transient ischemic attacks, normal neurological examinations and stenotic carotid vessels, can be benefitted in a high percentage of cases with little or no mortality or morbidity.

Patients with fresh cerebral infarcts or fixed neurological deficits have little chance of benefitting from carotid endarterectomy. Carotid endarterectomy should be considered prophylactic as related to neurological deficit and rarely carried out with the intent of improving a stable neurological abnormality.

An angiographic finding of one occluded and one stenotic carotid artery is a dangerous combination, and only if the clinical situation is favorable should surgical intervention be considered.

There is little benefit in operating upon completely occluded carotid vessels, because there is little evidence to suggest that the patient would benefit even if blood flow was restored.

Adequate intracranial vascular demonstration must be included in the angiographic work-up to avoid missing a primary or associated intracranial lesion.

A brief discussion is given of the possible mechanisms of transient ischemic attacks.

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About the only thing that comes to him who waits is whiskers.

Intact Vesicosigmoidoplasty

LEO CULLIGAN, M.D.* and T. H. SWEETSER, JR., M.D.*

PRESERVATION AND EXPANSION of the urinary bladder has been accomplished previously by the use of partial segments of bowel, patches of bowel or fascia, or by vesical regeneration[2] with or without prostheses. Techniques which involve bowel resection and reanastomosis are rather long and tedious and attended by some degree of morbidity and complications.[3] A recent report of a case using intact colon to expand the bladder capacity[4-7] seemed to answer many of the objections to prior procedures and was utilized in two cases.

*Departments of Surgery and Urology at St. Mary's Hospital, Minneapolis, Minnesota.

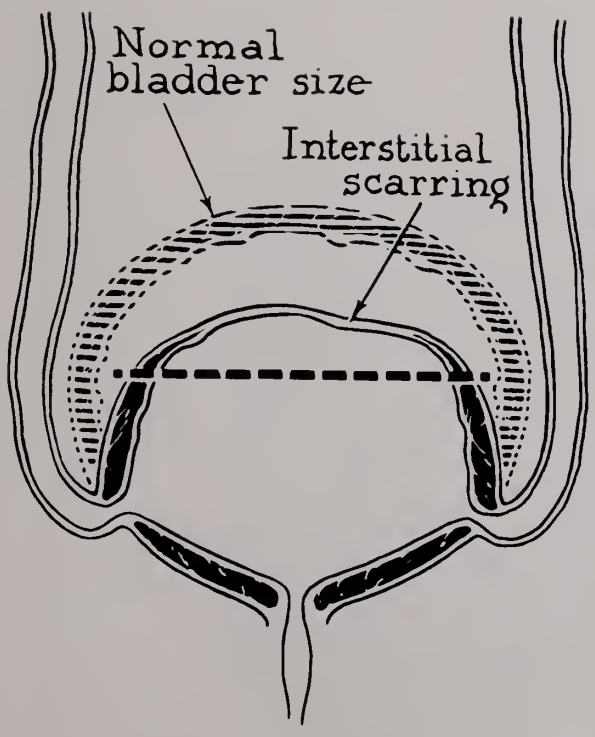


Fig. 1—Proposed line of excision of bladder involved with interstitial scarring.

Case Reports

Case 1

A 54-year-old white woman had undergone multiple hospital admissions for severe interstitial cystitis. Various forms of therapy had produced only modified and temporary relief. On her final admission, she was voiding at 15-minute intervals in amounts up to 30 cc. with pain and occasional urgency incontinence. Bladder capacity under anesthesia measured 80 cc. and cystoscopy revealed a markedly contracted bladder with normal mucosa evident only over the trigone and adjacent area. Abdominal exploration revealed the bladder fundus to consist of thin contracted scar tissue (Figure 1). An extensive segmental resection of the bladder was performed, leaving a small cuff of normal appearing bladder wall surrounding the trigone and vesical neck. Intact vesicosigmoidoplasty was performed, after which a two-wing Malecot catheter was left indwelling and removed on the tenth postoperative day. No complications ensued and three weeks following surgery the patient was voiding 180 cc. amounts with no pain or urgency. Cystoscopy nine months later revealed normal vesical mucosa covering the bowel serosa with no decrease in the area of the anastomosed segment. A postoperative excretory urogram revealed essentially normal upper urinary tracts with an improved cystogram; the patient was voiding normally with no residual urine or infection (Figure 2).

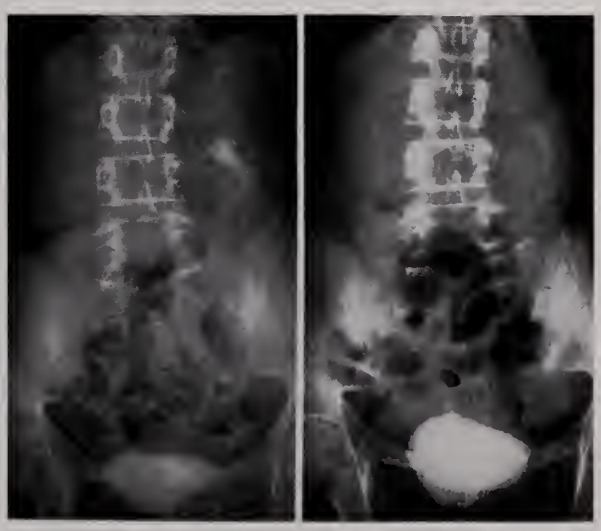


Fig. 2—Pre- and postoperative x-rays show good bladder capacity after procedure.

Case 2

A 72-year-old white man underwent a transurethral resection of a Grade I, stage I papillary carcinoma of the bladder in 1962. Recheck cystoscopies were negative until 1968 when massive recurrence of the tumor was noted which on resection proved to be Grade II, stage B_1 and extended over the entire dome of the bladder and much of the right lateral wall including the right orifice and edge of the trigone. Moderate right hydronephrosis was noted but no extension of the tumor could be palpated on rectal examination. His severe cardiovascular disease was increased by the marked tenesmus and lower abdominal pain associated with the tumor and unrelieved by medication. At operation, the bladder was found to be free of any palpable extension of the tumor. Extensive segmental resection was carried out including the distal 3 cm. of the right ureter and adjacent trigone and entire dome and right side of the bladder. The edges of the specimen were tagged and frozen sections obtained which showed some mucosal extension of the tumor near the anterior point of resection. A second segment was excised anteriorly down to the vesical neck which showed no residual tumor. The right ureter was reimplanted in the remaining trigone near the mid line (Figure 3). About 60% of the bladder was removed and the intact sigmoid was anastomosed to the remaining segment of the bladder. The catheter was removed on the 14th postoperative day and the patient voided with some frequency but without pain or difficulty. His cardiovascular status improved and he was discharged the following week. Three months later the patient was voiding up to 180 cc. at two-hour intervals, was free of symptoms and had as yet no evidence of recurrent tumor (Figure 4).

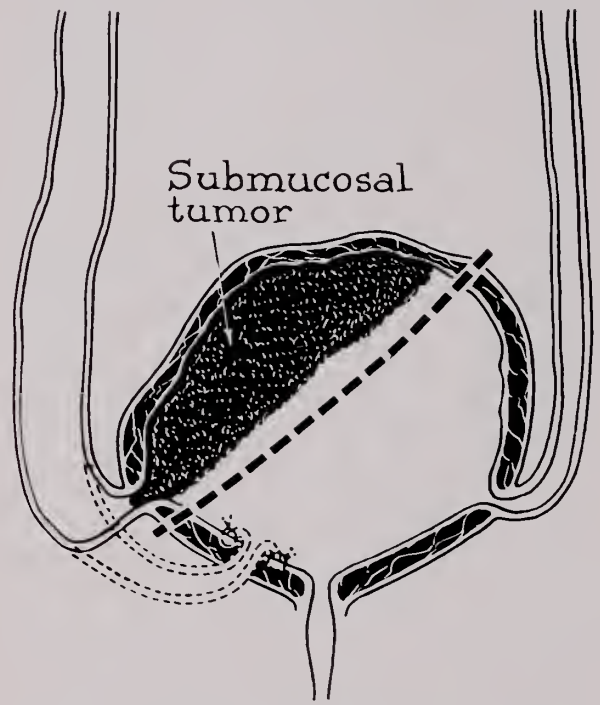


Fig. 3—Proposed line of resection of bladder involved with submucosal tumor. This together with the lower ureter was excised and the ureter was then implanted into remnant of bladder.

Operative Technique

Preoperative

Preoperative x-ray studies of the colon are indicated to rule out pathology and assure the presence of sufficient colon to permit mobilization without difficulty. Severe diverticulosis would seem to be a contraindication to this procedure. After mobilization, the appendices epiploicae in the area are removed to give a smooth serosal surface.

Excision of Diseased Portion

Excision of the diseased portion of the bladder is carried out as widely as necessary. Where a ureter is involved in the excision,

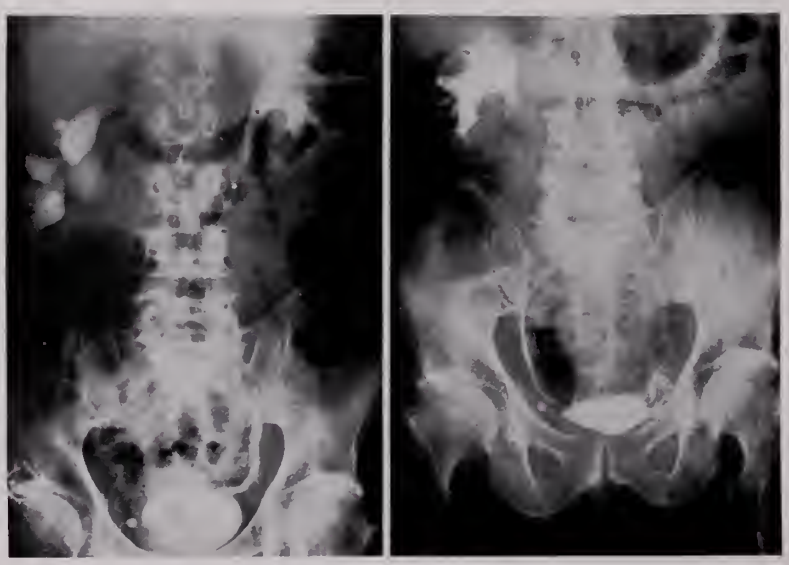


Fig. 4—Pre-and postoperative urogram reveals decrease in hydronephrosis and adequate bladder capacity after operative procedure.

either uretero-ureterostomy or ureteroneocystostomy can be utilized to preserve ureteral function (Figure 3).

On-lay of Sigmoid

Mobilization of the sigmoid colon and its blood supply to permit the repair without tension is first carried out.

The second portion of the procedure consists of replacing the bladder wall with the adjacent sigmoid colon by an on-lay procedure. The edge of the remaining bladder is sutured to the intact serosa of the colon, avoiding any deep suturing which could conceivably produce fistula formation.

Two rows of suture are used in anastomosing the bladder to the sigmoid colon—the outer row of 4:0 interrupted silk sutures closely placed with the knots tied on the outside of the anastomosis. The initial outer row of these is placed across the back wall of the bladder, joining the serosal surface of the bladder to the serosa of the colon (Figure 5A). While the bladder is still open prior to placing the front row of the chromic sutures, a Malecot catheter is inserted into the bladder under vision to assure proper placement and avoid any possible injury to the suture lines by blind introduction of a balloon catheter after closure. An internal inner row of fine chromic catgut is then used to encircle the mucosa of the bladder to the serosa of the sigmoid, utilizing the greatest possible width of the colon with sufficient length of sigmoid to replace the lost segment of the bladder (Figure 5A). A final row of interrupted silk sutures anastomosing the anterior portion of the bladder to the serosa of the colon completes the procedure (Figure 5B).

Two Penrose drains are placed on either side of the anastomotic site and brought out through the lower portion of the incision. In the cases presented, no urinary drainage has been noted postoperatively.

Discussion

In the treatment of bladder carcinoma, segmental resection has established results as good as more radical methods when the cases are carefully selected.[5] A main objection in the procedure is the submucosal spread of carcinoma beyond the visible tumor. The present procedure allows more extensive segmental resection without sacrificing adequate bladder capacity. Simple cystectomy with vesical regeneration would seem to have equal simplicity and preservation of function, but to date has been complicated by reflux and infection and holds no greater assurance against recurrent tumor.[6]

While the majority of contracted bladders respond fairly satisfactorily to more conservative therapy, a number of patients are left partially disabled and miserable with their disease and are unable to accept urinary diversion. The present procedure seems to offer some compromise in a difficult situation.

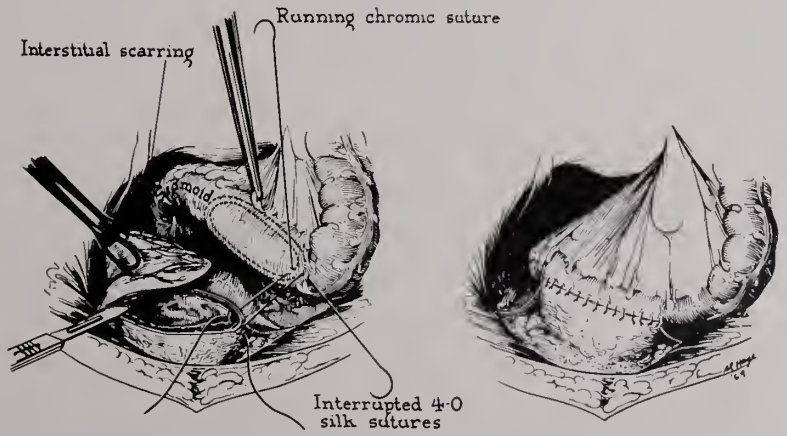


Fig. 5—(A-, left) shows the placing of an outer row of 4:0 silk sutures and an inner row of running 3:0 chromic suture joining the cut edge of the bladder to the serosa of the sigmoid colon. (B-, right) completed anastomosis.

Summary

The use of the serosa of the intact sigmoid colon to replace a vesical defect caused by extensive segmental resection was introduced in a previously reported case.[4] Further utilization of this procedure is described, including its use in severe interstitial cystitis as well as carcinoma of the bladder. The relative simplicity and rapidity of the procedure would suggest its continued use where large portions of bladder require replacement.

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THE SACROTUBEROUS-SACROSPINOUS SYNDROME

A CONSIDERABLE number of backaches seem to defy physical evidence of their existence. They can be functional, physiologic or organic.

The sacrotuberous-sacrospinous ligament syndrome is manifested by one-sided pain located below the sacroiliac joint adjacent to the lateral border of the sacrum and extending into the medial border of the gluteus area. It consists of a dull, aching pain which may radiate into the posterior thigh and is aggravated by walking and running or by any activity which may involve an alternating shift of weight. It is less evident in a correct standing or sitting position. A lop-sided posture is avoided because of the discomfort which results.

Occasionally the syndrome becomes evident after an accident; but more often there is no history of any injury or incident to which it can be ascribed.

The general physical examination is non-contributory, but the rectal examination yields the diagnosis: with the patient lying on his side in the embryonic position, pressure upon the sacrotuberous and sacrospinous ligaments, right and left, elicit unequivocal unilateral and exquisite tenderness on the involved side and reproduce the subjective symptoms.

Relief is often obtained almost immediately after these fan-shaped set of ligaments are firmly massaged with a palpating finger. Occasionally three or four such daily treatments provide complete relief. If relief is not so obtained, further search for a diagnosis becomes necessary.

Carl O. Rice, M.D.

The Man of the Future

If it keeps up, man will atrophy all his limbs but the push-button finger—Frank Lloyd Wright

Concomitant Opportunistic Infection

with

Toxoplasma Pneumocystis and Cytomegalovirus*

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PATIENTS WITH MALIGNANT neoplastic diseases, receiving cytotoxic chemotherapy, irradiation or adrenocorticosteroids are in a state of secondary immunologic incompetence, demonstrating an increased susceptibility to infections. The majority of the infections are caused by some common and some uncommon pathogenic bacteria and can usually be treated effectively with available antibiotics that induce significant alterations in the normal body microbial flora.

Many opportunistic organisms which are saprophytic in healthy individuals cause fatal infections due to immunologic deficiency and changes in microflora. Frequently more than one organism infects susceptible individuals, creating an extremely complex clinical picture. This problem is exemplified by the following case presentation of a patient who exhibited three concomitant opportunistic infections: toxoplasmosis, Pneumocystis carinii pneumonitis and cytomegalic inclusion disease.

Case Reports

First Admission

A 41-year-old white female was referred to the University of Minnesota Hospitals for evaluation of a chronic cyclitis and retinal vasculitis of three years' duration.

One month prior to referral the cyclitis had recurred and she was started on dexamethasone (Decadron) orally.

Physical examination revealed generalized lymphadenopathy and hepatosplenomegaly.

The hemoglobin was normal; the white blood cell count was 17,500 with 80% lymphocytes. A peripheral blood and bone marrow examination confirmed the diagnosis of chronic lymphocytic leukemia. A dye test for toxoplasmosis was positive in a titre of 1:64, and the complement fixation test for toxoplasma was negative. A Mantoux test and skin tests for blastomycosis, coccidioidomycosis and histoplasmosis were negative. A chest roentgenogram showed some calcification at the apex of the left lung. The Decadron was discontinued as the cyclitis improved; active therapy of the leukemia was not undertaken.

Second Admission

Fifteen months later the patient was seen again at University Hospitals because of persistent headache. Her pulse was 80, blood pressure 135/105, respiratory rate 16, and temperature normal. She was lethargic and inattentive but otherwise in no distress. A funduscopic examination revealed a vasculitis but no papilledema. There was generalized lymphadenopathy and hepatosplenomegaly. A neurologic examination was unremarkable.

The hemoglobin was 14 gm %, the white blood cell count 28,800 with 94% lymphocytes. A platelet count was 182,000 per cu. mm. Urinalysis showed traces of albumin; culture of the urine was sterile. Both a direct and an indirect Coombs test were negative. A chest roentgenogram was also negative save for the old calcification in the left lung.

Two weeks after her admission, vertigo, nausea and vomiting were associated with the headaches. Neurologic examination revealed nystagmus to the left and unsteadiness of finger-to-nose test on the left. Ear, nose and throat examinations revealed no abnormalities; caloric testing was normal. A cerebrospinal fluid examination was normal and sterile on culture. A brain scan and an echogram were unremarkable.

With the administration of prednisone the headaches disappeared and the patient remained symptom-free for three months. Thereafter she complained of weakness, and of abdominal distress from an enlarging spleen; and progressive anemia necessitated frequent blood transfusions. She received a two-week course of chlorambucil (Leukeran) and her white blood cell count fell to 4,000 with 90% lymphocytes. The dose of adrenocorticosteroids was increased in an effort to control hemolysis. After

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admission to a local hospital her spleen ruptured and was removed surgically. Her postoperative course was uneventful, and her white blood cell count rose to 80,000 with 90% lymphocytes. The thrombocytopenia and hemolysis persisted after splenectomy and the corticosteroid dosage was increased.

Third Admission

Because of increasing abdominal distention and increasing weakness, the patient was transferred to University Hospital where she again exhibited generalized lymphadenopathy, hepatomegaly, and an abdomen markedly distended with ascitic fluid. The hemoglobin was 7.2 gm %, the white blood cell count 86,000 with 87% lymphocytes and platelets decreased to 10,000 per cu. mm. Her blood urea nitrogen was 42 mg. per 100 ml. and creatinine 0.7 mg. per 100 ml. On the third hospital day she spiked a temperature of 101°F and thereafter remained febrile throughout the hospital course. Cultures of blood, ascitic fluid and cerebrovascular fluid remained sterile. On the sixth hospital day she became confused and disoriented. Her blood pressure dropped and she was given blood transfusions. On the eighth hospital day she received cyclophosphamide (Cytoxan) intravenously. Two days later she was placed on penicillin and kanamycin (Kantrex) initially and erythromycin and sodium cephalothin (Keflin) later. Corticosteroids were administered in massive doses. A chest roentgenogram, four days before death, showed diffuse bilateral, interstitial and alveolar infiltrates without cardiomegaly. Only a few scattered rales were present in the lungs. She died 17 days after her admission and approximately two years after the diagnosis of chronic lymphocytic leukemia.

Autopsy

Macroscopic Pathology

On gross examination, petechiae and ecchymoses were present over the skin and moderate pitting edema on both legs. Generalized lymph node enlargement was noted. There were about 100 ml. of clear yellowish fluid in each pleural cavity and a large amount of sanguinous fluid in the abdominal cavity. The heart weighed 210 gm. and showed no gross abnormalities. Both lungs were heavy and generally firm with many patchy areas of pale greyish consolidation. The liver showed an accentuated lobular pattern and passive congestion. The brain appeared normal.

Microscopic Pathology

On microscopic examination, in addition to the lymph nodes, the liver and lungs were involved with the leukemic process. Sections of the lungs showed honey-combed, foamy, vacuolated intra-alveolar material containing Pneu-

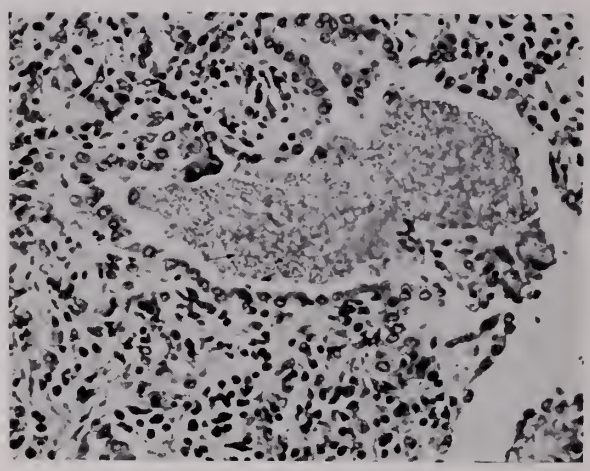


Fig. 1—Lung section. Small black dots (arrow) represent Pneumocystis carinii within foamy material in the alveolus. Hyperplastic alveolar cells contain intranuclear inclusion bodies (arrow). There is marked leukemic lymphocytic infiltration in the alveolar septa. Hematoxylin and Eosin stain x 400.

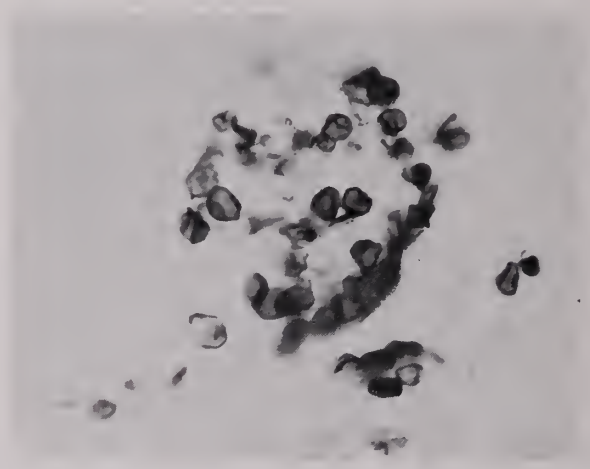


Fig. 2—Lung section. A cluster of Pneumocystis carinii organisms within an alveolus. Grocott-Comori Methenamine Silver Nitrate Stain. x 1000.

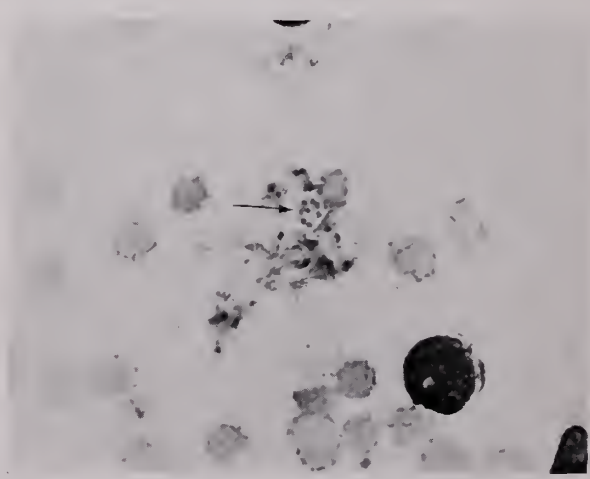


Fig. 3—Lung imprint, air-dried. Pneumocystis carinii cyst with 8 bodies (arrow). Giemsa stain. x 1000.

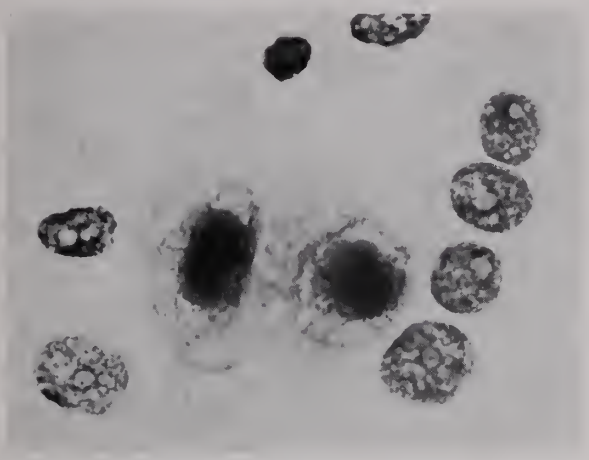


Fig. 4—Lung imprint, air-dried. Intranuclear inclusion bodies. Giemsa stain x 1000.

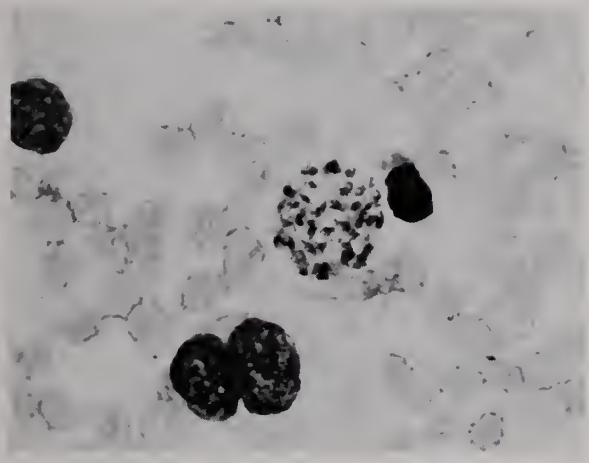


Fig. 5—Lung imprint, air-dried. Toxoplasma gondii cyst. Giemsa stain x 1000.

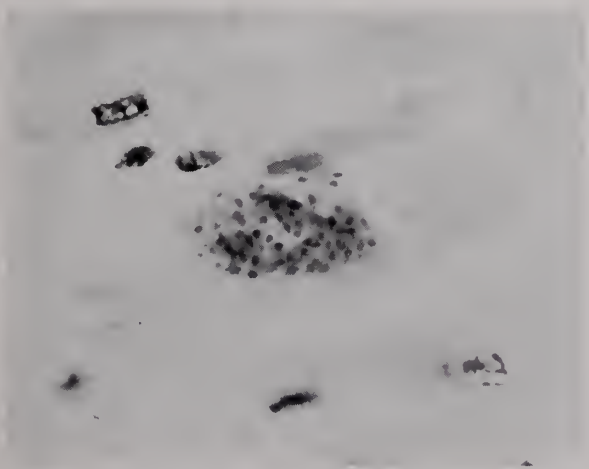


Fig. 6—Heart section. Toxoplasma gondii cyst within myocardial fiber. Hematoxylin and Eosin stain x 1000.

mocystis carinii organisms (Figure 1). Pneumocystis cysts were also demonstrated in Grocott-Gomori methenamine-silver nitrate-stained sections and in Giemsa-stained air-dried imprints of the lungs (Figures 2 and 3). In sections and in air-dried imprints of the lungs, enlarged cells with typical cytomegalovirus intranuclear inclusion bodies were seen (Figures 1 and 4). Cytomegalic cells were also found in the ovary, myometrium, cervix, and lymph nodes. Air-dried imprints of the lungs showed a few large cells containing numerous crescent-shaped Toxoplasma gondii organisms (Figure 5). Vegetative Toxoplasma cysts were not found on sections of the lungs, but cysts were found within myocardial fibers (Figure 6) and in the brain near foci of necrosis and microglial reaction.

Discussion

Infections with opportunistic organisms superimpose a wide spectrum of manifestations on the already complex clinical picture of the underlying malignant disease. With mixed infections the problem of antemortem diagnosis becomes even more difficult. The importance of an accurate diagnosis cannot be overstressed since many of these opportunistic infections are treatable and potentially curable. When the clinical picture justifies the search, the diagnosis of one infection should not preclude the efforts to discover coexisting disease.

Toxoplasmosis

A symptomatic infection with Toxoplasma gondii can manifest mainly glandular involvement, remain a localized disease limited to one organ, or act as a miliary infection involving many organ systems.[1] The diagnosis can be established indirectly by finding rising or falling titres of Toxoplasma antibodies, or directly by identifying the parasite in biopsy sections and isolating the organism after animal inoculation of biopsy material or body fluids.[2]

Pneumocystosis

The Pneumocystis carinii organism has been considered to have a remarkable tissue specificity causing only infection of the lungs with a diffuse bilateral interstitial alveolar type of pneumonitis and inducing an alveolar-capillary

block.[3] However, cases of disseminated pneumocystosis have been recently documented.[4,5] The diagnosis can be established by demonstrating the organisms in the sputum, in hypopharyngeal and bronchial aspirates or washings, and in percutaneous or open lung biopsy sections or imprints.[6] Lymph node biopsy might turn out to be helpful for the diagnosis of disseminated pneumocystosis. A complement fixation test has been introduced but it needs additional evaluation.

Cytomegalovirus Infection

Cytomegalovirus can cause a prenatal or postnatal infection with a wide variety of symptoms and findings.[7-10] Infants with the prenatally acquired disease present with jaundice, hepatosplenomegaly, hemorrhagic diathesis due to thrombocytopenia, microcephaly, chorioretinitis and psychomotor defects. In the survivors, stigmata of the intrauterine infection such as intracerebral calcifications, deafness, spasticity, and epileptiform seizures appear in later years. Children with the postnatal infection present with fever, cough, pneumonia, diarrhea, jaundice, hepatosplenomegaly, hemolytic anemia, leukopenia and thrombocytopenia. In children and adults with neoplastic disease a fatal myocarditis,[11] severe pneumonia,[11-13] gastrointestinal ulcerations and bleeding,[11] and adrenal insufficiency from adrenal necrosis[12,13] have been attributed to cytomegalovirus infection of the respective organs.

An infectious mononucleosis-like illness with a negative Paul-Bunnell test in the immunologically competent individual can be caused by cytomegalovirus.[14-20] This type of the infection is generally characterized by prolonged fever and malaise without pharyngitis or tonsillitis. Many of these cases show lymph node enlargement, and liver involvement is uniformly present. Splenomegaly was present in one third of the patients in one series.[19] Myocarditis, pericarditis, bronchopneumonia, polyneuritis and hemolytic anemia have been observed. The typical mononucleosis or Downey type cells were seen in the blood of most patients. In certain instances the manifestations of hepatitis dominated the clinical picture.[16-18] A variety of other manifestations have also been observed, such as severe headaches, conjuctivitis, exanthema, gastroenteritis, and vaginitis.

The diagnosis of cytomegalic infection is established by demonstrating the cytomegalic cells in saliva, sputum, urine or gastric washings by exfoliative cytologic techniques or in biopsy specimens of liver, lung and lymph node or by isolating the virus in cultures of various cell lines inoculated with body fluids or biopsy tissue specimens. Changing antibody titres detected by the complement fixation technique and the neutralization technique provide another diagnostic method.[19]

Coexisting Disease Syndromes

Simultaneous toxoplasmosis and cytomegalic inclusion disease has been observed with unexpected frequency[21-23]; occasional cells were found to be infected concomitantly with the protozoon and the virus.[21] This double infection of the same cell has been reproduced in vitro in culture of human fibroblasts.[24] The coexistence of pneumocystic carinii pneumonitis and cytomegalic inclusion disease has been reported and reviewed repeatedly; cytomegalic inclusion disease seems to be the most common opportunistic infection associated with pneumocystic carinii pneumonitis.[25-28] Concomitant toxoplasmosis and pneumocystic carinii pneumonitis has been described by one of us.[6] However, the simultaneous infection with all three organisms as observed in this patient has not been previously reported.

It should be emphasized that the organisms and the characteristic cells were seen at autopsy on air-dried Giemsa-stained imprints of lung. With the imprint technique the diagnosis might be made earlier than with paraffin sections. Therefore imprints should be made of any lung biopsy specimen when opportunistic pulmonary infection is suspected.

Summary

A patient with chronic lymphocytic leukemia developed a bizarre clinical syndrome characterized by severe headaches, vertigo, nausea and vomiting. This improved with prednisone, but a subsequent febrile illness with interstitial pneumonitis caused the patient's death. Pneumocystic carinii pneumonitis, systemic toxoplasmosis and cytomegalic inclusion disease were found at autopsy. The organisms and the

characteristic cells were seen on air-dried imprints of lung.

Imprints of lung biopsy specimens may facilitate earlier diagnosis of opportunistic lung infections. In the presence of secondary immunologic deficiency states such infections are often multiple. The concomitant infections with Toxoplasma, Pneumocystis and Cytomegalovirus are reported for the first time.

Generic and Trade Names of Drugs

Dexamethasone	—	Decadron
Chlorambucil	—	Leukeran
Cyclophosphamide	—	Cytoxan
Kanamycin	—	Kantrex
Prednisone	—	Meticorten
Sodium Cephalothin	—	Keflin

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E. M. Pooley gave his version of allergy to the readers of the El Paso, Texas Herald-Post:

You get sick nowadays and what you got? Either a virus or an allergy. A virus is what you got when the doctors don't know what you got. An allergy is what you got when the doctors know what you got but don't know where you got it. The other morning I was awakened by a full-fledged case of the hives.

"Must be something you et," says the doc. "You got an allergy." Then the young doc explains it all.

He says that when the pithecanthropus of the eudaemon is in juxtaposition with the translux it makes a hyperthyroid excrescence that combines with the whatnot and brings about psoriasis of the membrane and an irritation of the callipygian exodont. In other words, you itch.*

*Dr. Francis Leo Golden: Jest What the Doctor Ordered.

Humanities

Excelsior!

Social history contains many stories of debacles resulting from blind or obstinate resistance to change, but it is also replete with examples of triumphant adaptation and mutation. On an individual basis we all admire persons who, having come from one culture as an immigrant for example, make a successful adaptation to a new environment, and we are likely to condemn the person who cannot or does not adapt. Doctors individually and collectively face this kind of challenge and choice.

In picturing the personal predicament of the physician, although my colleagues may find it rather cold comfort, I have tried to do as the artist Van Gogh, who stated, "When I paint a picture, I try to say something comforting."

In this spirit and at the risk of presumption, I should like to cite two passages from Tennyson, a poet with a particular sensitivity to the personal losses resulting from change and one who knew the suffusing personal optimism which followed the individual resolution of such loss.

The first passage is from *Morte D'Arthur,* wherein King Arthur's dying signifies the end of an era. One of his disconsolate retinue, the bold Sir Bedivere appeals to him for counsel, asking, ". . . whither shall I go?" and adds, "For now I see the true old times are dead . . ." The departing Arthur answers:

> The old order changeth, yielding place to new;
> And God fulfills himself in many ways,
> Lest one good custom should corrupt the world.
> Comfort thyself: what comfort is in me?

The last line echoes Arthur's awareness that the old order which he embodies cannot provide for the present, much less the future. But Tennyson has more than this to say to us about adapting to change. In *Ulysses,* as the aging king soliloquizes about his now quiet life in contrast to the dreams and accomplishments of his youth, he explains his resolve to strike out again to new adventure and:

> To follow knowledge like a sinking star,
> Beyond the utmost bound of human thought.

As he greets his old seafaring comrades at the shore before starting off, he shares his dream with them:

> You and I are old . . . but something ere the end
> Some work of noble note may yet be done,
> Not unbecoming men that strove with the Gods.

Then Ulysses assumes his customary role of leadership, saying:

> Come my friend. 'Tis not too late to seek a newer world.

If we physicians are to assume leadership in medical affairs, we too must go forward to a newer world.*

Magraw, Richard: Ferment in Medicine, 1966.

Money will buy a fine dog, but only love will make him wag his tail.—Ulster Post

Breathing Retraining

Mount Sinai Hospital

Emphysema-Chronic Bronchitis Clinic

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BREATHING RETRAINING is a useful modality in the rehabilitation of patients with chronic obstructive lung disease. The goal of these exercises is to help the dyspneic patient breathe more effectively so that he can maintain adequate pulmonary ventilation at a given level of activity. Basically, breathing retraining consists of teaching the patient to perform extended exhalations through pursed lips, using the abdominal muscles to move the air.

Strengthening the Abdominal Muscles

Use of the abdominal muscles is the key to the training procedure. Therefore abdominal strengthening exercises enable the patient to concentrate upon this musculature.

Sit-Ups

This is the exercise of choice. The patient assumes the supine position and then sits up. Assistance may be needed if he is weak. If he reports pain in his back or at the back of his knees when doing the sit-up, flexion of the knees will ease this during the exercise. This exercise is repeated five times twice each day.

Neck Flexions

This exercise is for patients who cannot tolerate sit-ups. The patient lies on his back, lifts his head and shoulders and then holds for a count of five. This is repeated five times twice daily.

Pelvic Tilts

This very gentle form of abdominal strengthening exercise is done in the standing or lying position. In the supine state, the knees are slightly flexed, the pelvis is tilted so that the small of the back moves toward the table and the pubic area lifts more vertically. The same maneuver may be performed in the standing position with knees fully extended.

In the Supine Position

The patient places his right hand on his abdomen just below the ribs and his left hand on his upper chest. The hands act as guides to help him determine which part moves. He then tightens the abdominal muscles slowly and gently to exhale and relaxes them to inhale. After two or three repetitions he is asked to perform extended whistling as he exhales. After each whistle he is instructed to inhale a small amount of air "into the belly only." In many instances, the patient can extend the

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whistle eight to 10 seconds. It must be stressed that he not "puff up" his chest.

In the Standing Position

The patient stands with his hands hanging at his sides or clasped in front in a relaxed position. He then performs the previous maneuver. He is encouraged to relax his shoulders. This may be made easier by placing his hands in his pockets or by gentle downward and forward pressure on his shoulders by the therapist. He may stand in front of a mirror in order to watch for and avoid shoulder motion with respiration.

Variations of Techniques

The extremely tense patient who cannot sufficiently relax his abdominal wall for inhalation may begin his training in the side-lying position with the hips, knees and elbows in a flexed position.

Timing

Correct timing is of great importance in achieving the desired relief. Exhalation must be sufficiently prolonged to expel some of the stale air; however, it should not be so long that the patient has to work very hard, becomes "blue in the face" or feels he must take a big breath. Most patients can achieve a five-ten second exhalation with a one-two second inhalation.

Whistling

It must be stressed to the patient that whistling or exhaling through gently pursed lips serves an important purpose by encouraging a longer exhalation and probably maintaining airway patency. Each whistle should last at least five or preferably eight to ten seconds. The patient will often find he can "turn off the wheeze" if he whistles.

Innovations

Other "tricks" which may be useful in breathing retraining are: Bending a candle flame: With the patient sitting or standing, a candle is held six to 18 inches in front of him. He is instructed to blow and try to "bend the candle flame" without putting it out. This helps him avoid an initial gust of air and thus enables him to extend exhalation.

Lifting the head from the pillow with exhalation and replacing the head back on the pillow with inhalation.

Using a metronome to help establish correct timing: With the metronome set at 60 beats per minute, many patients will be able to whistle for eight-ten beats and breathe in for one-two beats.

Looking at the floor and standing in a relaxed and slightly slouched manner with the hands in his pockets, the patient will be able to perform the abdominal breathing exercises more easily.

Conclusion

The patient who is able to do abdominal breathing through pursed lips on a regular basis will ventilate his lungs more efficiently. Since this method of breathing is quite different from the normal breathing pattern, persistent instruction and reported supervised practice will be necessary if the patient is to learn the skill well enough to achieve the desired relief.

I have but one lamp by which my feet are guided, and that is the lamp of experience.—Patrick Henry

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Perseverance

Perseverance is the most overrated of traits, if it is unaccompanied by talent; beating your head against a wall is more likely to produce a concussion in the head than a hole in the wall.—Sydney Harris

Temporal Arteritis

A Case with Abdominal Aortitis Presenting As A Malignancy

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A HISTORICAL REVIEW of the early descriptions and nomenclature of temporal arteritis reveals the remarkable changes that have occurred in the comprehension of this disease. The first clinical description of temporal arteritis was made by Hutchinson[1] in 1890 when he reported the case of an 80-year-old man who complained he could not put on his hat because of painful swelling of his temples. However, it was not until the report of Horton and co-workers[2] in 1932 of two cases of "arteritis of the temporal vessels," describing the histologic appearance of the arteries, that temporal arteritis was recognized as a distinct clinicopathologic entity. In 1941 Gilmour[3] reported four cases of nonspecific arteritis involving the aorta and other large vessels. The histologic appearance of the arteries in these cases was similar to that described in Horton and associates' report of temporal arteritis. Multinucleated giant cells were abundant; consequently the disease was named "giant-cell arteritis."

The term "cranial arteritis" was introduced by Kilbourne and Wolff[4] in 1946 because they were impressed with involvement of the cerebral and ophthalmic arteries. In the same year, Cooke and co-workers[5] advanced the concept that temporal arteritis was a widespread arterial disease which most often affected the temporal arteries. Subsequent authors[6-9] have confirmed this observation.

More recently Alestig and Barr[10] demonstrated giant-cell arteritis on biopsy of asymptomatic temporal arteries of some patients with polymyalgia rheumatica. This is a clinical entity which affects older patients and has been given a variety of names. It is characterized by muscular pain and stiffness and an elevated erythrocyte sedimentation rate. In the belief that temporal arteritis and polymyalgia rheumatica were both manifestations of a systemic disease, Hamrin and co-workers[11] introduced the term "polymyalgia arteritica" to link the two disorders. The various organ manifestations of temporal arteritis have been outlined by Paulley and Hughes[12] and by Andrews;[13] however, symptoms due to arteritis of vessels other than the temporal arteries have been uncommon.

The following case report describes a patient whose disease masqueraded as malignant, until arteritis involving the abdominal aorta was found at the time of exploratory laparotomy.

Report of Case

Myalgia and Headaches

A 68-year-old white male farmer came to the Mayo Clinic on September 11, 1967, for evaluation of complaints of abdominal pain and anorexia of two months' duration. Except for aching and tenderness of the muscles of his neck and shoulders for approximately three months in 1966, this patient had been well until May, 1967, when he experienced the onset of severe steady aches in the left parietal area of the head and noticed that his scalp was slightly tender when he combed his hair. Aspirin gave temporary relief, but the headaches persisted for approximately eight weeks before subsiding completely.

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Claudication of the jaw and changes in visual acuity were not apparent. Because of the headaches and general malaise, the patient consulted his local physician in July, 1967. A normochromic normocytic anemia was found; but roentgenograms of the gastrointestinal tract and an electrocardiogram were interpreted as normal, and examination of the cerebrospinal fluid gave negative results.

Abdominal Distress

As the headaches subsided, the patient began to notice constant pain in the right lower quadrant of his abdomen, aggravated by food which seemed to "block" in the right lower quadrant. Consequently he began to eat small liquid meals. Partial relief from the abdominal pain was obtained by ingestion of aspirin or by lying prone. Nausea, vomiting, and change in bowel habits were denied, but the anorexia and restriction of caloric intake resulted in a weight loss of 20 pounds.

Fever

On August 29, 1967, he was hospitalized elsewhere and was found to have a daily low-grade fever up to 101° F. Because of some abnormalities noted on an excretory urogram and oral cholecystogram, abdominal exploration was recommended for presumptive diagnosis of a retroperitoneal lesion and cholelithiasis. The patient was referred to this clinic for further evaluation.

The patient was 69 inches tall and weighed 135 pounds. He appeared chronically ill and had a sallow complexion. The blood pressure measured 118/60 mm Hg; the pulse rate was 68 beats/min, and the temperature was normal. The optic fundi appeared normal on examination. The arterial pulses were also normal, except for a slight diminution in the pulsations of the temporal arteries bilaterally and an absent right dorsalis pedis pulse. No tenderness or swelling of the temporal arteries was observed. Examination of the chest revealed hyperresonance, scattered rhonchi, and limited expansion (one inch). The clinical diagnoses were emphysema and possible carcinoma of the pancreas; efforts to exclude hypernephroma or lymphoma were thought appropriate.

Laboratory Studies

Laboratory data follow: specific gravity of urine 1.028, proteinuria grade 1, erythrocyturia grade 2, pyuria grade 1, glycosuria 0, and occasional hyaline and granular casts in the urinary sediment; blood hemoglobin 10.0 gm/100 ml; red blood cells 3.77 million/cu mm; leukocytes 8,700/cu mm—lymphocytes 20.5%, monocytes 6.5%, neutrophils 71.5%, eosinophils 0.5%, and basophils 1.0%; erythrocyte sedimentation rate 100 mm in one hour (Westergren); prothrombin time 21 seconds (normal 17 to 19); sulfobromophthalein (BSP) dye retention after one hour 8%; alkaline phosphatase 106 U/liter (normal to 99); normal concentrations of blood sugar, urea, and lipase, of serum bilirubin, and of plasma cholesterol; a serologic test for syphilis (VDRL), a lupus erythematosus clot test, and a flocculation test for rheumatoid factor gave normal results; serum protein electrophoresis: albumin 1.83 gm/100 ml, α_1-globulin 0.44, α_2-globulin 1.09, β-globulin 0.83, Gr. gamma-globulin 1.00, and total protein 5.18.

Pulmonary function studies revealed a slight diminution of the forced vital capacity, compatible with mild emphysema. A roentgenogram of the chest was interpreted as showing torsion of the aorta. Oral cholecystography revealed a normally functioning gallbladder with cholelithiasis. Roentgenographic examinations of the esophagus, stomach, and duodenum and an excretory urogram were interpreted as normal. An electrocardiogram showed right ventricular conduction delay with a QRS interval of 0.10 second.

Retroperitoneal Edema

On September 18 a laparotomy was performed. Approximately 400 ml of straw-colored fluid was present within the abdominal cavity. The most striking abnormality was diffuse edema of the retroperitoneal structures, extending from the hemidiaphragms to the rim of the pelvis. Further examination revealed a ligneous subacute inflammatory reaction involving the aorta from the inferior border of the pancreas to the bifurcation of the common iliac arteries. The size and configuration of this portion of the aorta were not unusual; the inflammation did not extend into the mesenteric vessels or laterally to involve the ureters. The aorta was not biopsied, but lymph nodes were excised from the regions of the aorta and the hepatic artery. Cholecystectomy was performed.

Histologic examination of the lymph nodes showed nonspecific inflammatory changes. A rectus muscle biopsy was normal. Culture of the free peritoneal fluid grew a *Corynebacterium* species, but culture of the lymph nodes showed no growth.

Because of the surgical findings and the past history of severe headaches, biopsy of a temporal artery was performed. One branch of the artery appeared to have some thickening of the wall and the other appeared white and lusterless as though thrombosed. Histologic findings were consistent with a diagnosis of temporal arteritis.

Steroid Therapy

Steroid therapy was started immediately, the patient receiving oral prednisone, 40 mg daily in divided doses. Rather prompt and dramatic clinical improvement resulted with a gradual disappearance of the right lower quadrant pain and with a return of the patient's appetite and sense of well-being.

Comment

In retrospect, the initial aspects of this patient's illness were typical of temporal arteritis. The severe headaches, normochromic normocytic anemia, elevated erythrocyte sedimentation rate, and change in serum proteins are frequently seen in this disorder. Several months after the headaches disappeared, the diagnosis of temporal arteritis was established by biopsy of the then (clinically) normal temporal arteries. Although pathologic proof of giant-cell arteritis of the abdominal aorta is

lacking because biopsy of this vessel was deemed too hazardous, it is reasonable to believe that histologic examination would have confirmed the diagnosis. This presumption is supported indirectly by the absence of the rheumatoid factor, the negative results of the serologic test for syphilis and lupus erythematosus clot tests, and the lack of evidence for periarteritis nodosa on microscopic examination of rectus muscle and gallbladder.

Severe Complications

Although giant-cell arteritis most commonly is manifest in association with involvement of the temporal arteries, it can produce a multitude of symptoms by affecting many organs. A most feared complication is sudden blindness which may occur in about 40% of cases of classical temporal arteritis in which the ophthalmic arteries are involved.[14] Fessel and Pearson[15] have emphasized the danger of blindness in polymyalgia rheumatica. Cerebral vascular disease with hemiplegia and other neurologic symptoms and signs has been reported and can be fatal.[9,16] Angina pectoris[17] and myocardial infarction are also thought to be related,[13] since in some cases involvement of the coronary arteries has been demonstrated histologically.[5,9] Gangrene of the lower limbs,[18] changes in the skin and mucous membrane,[13] intestinal gangrene,[19] and renal failure[20] are rare complications. The symptoms and signs suggest malignant disease or infection, as illustrated by the case reported.

Microscopic evidence of giant-cell arteritis involving the thoracic and abdominal aorta is well known, having been reported by Sproul and Hawthorne[21] in 1937 under the name of chronic diffuse meso-aortitis; indeed, it has been said to be present in practically every case of temporal arteritis adequately examined histologically.[22] The complications of aortic-arch syndrome,[23] aneurysm formation, and aortic dissection with rupture[24] have been reported. In two instances successful surgical repair of thoracic aortic aneurysms has been performed.[25,26] The aortic-arch syndrome is also known to occur in polymyalgia rheumatica.[27]

References may be secured from the author or the reprints.

Although there was no evidence of involvement of the thoracic aorta in our case, the findings show that symptomatic arteritis can also affect the abdominal aorta, a manifestation less frequently reported than thoracic aortitis.

Ainsworth and Gresham[28] reported two cases of giant-cell arteritis in which death was due to aortic rupture. One patient was an 82-year-old woman who died suddenly after the onset of severe abdominal pain. At autopsy, a large fusiform aneurysm extending from the arch of the aorta to the beginning of the abdominal aorta was found; massive hemorrhage into the posterior mediastinum and retroperitoneal tissues had occurred. The exact site of rupture was not determined. Angiographic evidence of an abdominal aortic aneurysm above the bifurcation was described by von Knorring and coworkers[29] in the case of a patient who interestingly had both polymyalgia and concurrent temporal arteritis. Gilmour[3] described a patient who had a mass in the epigastric region: At laparotomy the abdominal aorta was found to be dilated; and eight months later autopsy revealed chronic arteritis of the aorta, which had healed almost completely. There was no evidence of aneurysm.

We thought our case merited reporting because involvement of the abdominal aorta in temporal arteritis, giving rise to clinical symptoms, is unusual. Furthermore, the findings emphasize the possibility of involvement of other arteries in cases of temporal arteritis associated with obscure pain problems.

Summary

A case of temporal arteritis in a 68-year-old man who presented with abdominal pain, malaise, fever, and loss of weight—simulating retroperitoneal malignant disease—is reported. Laparotomy revealed aortitis involving most of the abdominal aorta, ascites, and marked edema of the retroperitoneal tissues. A past history of headaches prompted temporal-artery biopsy which disclosed giant-cell arteritis. The aortitis was thought to represent similar involvement of the abdominal aorta, producing an unusual clinical syndrome.

Prosperity is only an instrument to be used, not a deity to be worshipped—Calvin Coolidge.

Assisting Survival*

The question of the ethics of pronouncing the patient dead becomes most acute when there is a need for a living organ for transplantation purposes; but this is not the only situation in which an ethical problem arises. Even more frequently, in fact, the question of whether or when one should properly "let a patient die," arises in medical practice. For example, after massive cerebral damage due either to so-called strokes or to trauma, patients may be assisted in survival by various means. In this situation the ethical problem is two-fold. Is it ethically proper to withhold treatment that might prolong life, is one question. But the opposite question, is it ethically proper to prolong mere survival when it is highly improbable that the person will ever be more than a "vegetable" if he or she is kept alive, is equally pertinent.

To deal with the organ donor problem first, the consensus among persons who have considered the problem, including philosophers, lawyers, physicians, clergymen and others, appears to be that under no circumstances should a physician who has an interest in obtaining transplantable material be a party to decision-making as to the potential viability of a possible donor. The physician or physicians who make this decision should not be interested parties to the availability of the patient's organs for other uses.

The concepts of ethicality and legality are intertwined, I may point out as an aside, because a large segment of law is concerned with ethical behavior. It can be thought of as a codification and an enforcement mechanism for rules of ethical behavior for individuals in contemporary society. Law as it applies to medical practice and medical research is largely a codification of what society today considers to be proper and moral in these areas. Consequently when one speaks of ethics in this arena one is also speaking about what ought to be law.

An example of a controversial matter is the employment of a new prosthetic device such as an artificial heart, an issue which happens to be one in controversy at the present time. At the time of preparing this essay I have on my desk a set of documents relative to a recent case in which such a device was implanted, and serious—I might perhaps say "accusatory"—questions are raised as to the ethical propriety of the performance of the surgeon who performed the experiment. I am being asked—as I suppose another large number of investigators are—to express my views about this particular case. I may say that it is not my intention to express any firm opinion on this case because I do not believe that I have had access to all of the facts. My own personal view is that all human trials of heart transplants and implantation of substitute mechanical hearts are premature at this time, but I am unwilling to call them immoral, if truly uncoerced and informed consent of the patient has been obtained by the experimenting surgeon. There is unquestionably a wide range within which ethical justifiability can be argued: a great grey area

*Presented at the Annual Meeting of the Association for the Coordination of University Religious Affairs, November 11, 1969.

of uncertainty between the poles at which either propriety or impropriety can be agreed upon with virtual unanimity. It is probably unwise to attempt to close this gap without more experience. The newness of the problem of establishing firm ethical and legal guidelines requires that great caution be used in fixing rigid rules to cover all exigencies.

Another area of great current interest is that of drug testing. The scientific-technical explosion of the twentieth century has brought within the grasp of man a fantastic array of chemical tools capable of modifying nearly every aspect of the behavior of living organisms. Increasing knowledge of biochemistry and physiology has been coupled with an increased capacity for chemical synthesis of new biologically-active compounds as well as an increased accuracy of prediction of their chemical activity upon enzyme systems and metabolic processes generally. A few each year show promise and must be tested in humans if they are ever to be employed in medical practice. After chemical and lower animal screening, human subjects must be employed because there are species differences in drug effects and also because specific disease conditions for which a drug might be useful may be difficult or impossible to duplicate in lower animals.

Here innumerable ethical problems arise. Parenthetically I would like to note that there is a small segment of society, so zoophilic and misanthropic in sentiment that they would prohibit drug toxicity testing in lower animals. They maintain, or perhaps only pretend to maintain, that all drug toxicity testing should be performed on human subjects! However, one can probably ignore this perversion of sentiment because, despite the cries of pet-lovers against the use of lower animals in medical research, most sane people mean simply that they would object to having their own pets so used. Only a few fail to recognize that in the ethos of human society as we know it, lower animals may be used in humane ways for the benefit of man. We would have to abandon our carnivorous practices first of all if we were to adopt another viewpoint. It does not seem likely that the human race will go vegetarian in the next generation at least, unless the population explosion makes race survival dependent upon eliminating the food waste involved in using domestic animals as converters of plant products into the more palatable animal foods.

But to return to the drug-testing theme, there are two important ethical problems. One is as to how extensive and exhaustive testing in man should be before physicians generally should be allowed to prescribe a new drug. The other is as to how much risk one is justified in asking a volunteer subject to undergo to test a drug's safety and efficacy. To neither question are there facile answers that satisfy all cases. There are, of course, easy answers, but all of them have flaws and are, in essence, false.

In this essay I have outlined only some of the current problems in ethics facing physicians and medical scientists today. I have sketched out some illustrative cases without pretense of exhaustiveness. My purpose has been to start cerebration on the basis of the realities of our present condition and to warn anyone who does think about the matters in question that, as in many other spheres of human concern, decisions as to what is good and proper, and what is not, will not be easy to come by.

Maurice B. Visscher, Ph.D., M.D.*
Minneapolis, Minnesota

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Supported by the Louis W. and Maud Hill Family Foundation.
See Part I in the April issue, page 367 and Part II in the May, issue, page 494.



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Dosage and Administration: *In the Female.* One 250-mg. tablet orally three times daily for ten days. Courses may be repeated if required in especially stubborn cases; in such patients an interval of four to six weeks between courses and total and differential leukocyte counts before, during and after treatment are recommended. Vaginal inserts of 500 mg. are available for use, particularly in stubborn cases. *When the vaginal inserts are used* one 500-mg. insert is placed high in the vaginal vault each day for ten days and the oral dosage is reduced to two 250-mg. tablets daily during the ten-day course of treatment. Do not use the vaginal inserts as the sole form of therapy. *In the Male.* Prescribe Flagyl only when trichomonads are demonstrated in the urogenital tract, one 250-mg. tablet two times daily for ten days. Flagyl should be taken by both partners over the same ten-day period when it is prescribed for the male in conjunction with the treatment of his female partner.

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Editorials

Lung Cancer*

In his article, "Therapy for Carcinoma of the Lung," Humphrey has emphasized the inadequacy of presently available therapy for most patients with this disease. Most of these cancers are not detected until symptoms have developed, and many of them cannot be resected. Of those patients whose cancer can be resected, less than half survive five years. This is tragic because most of these cancers, now causing about 60,000 deaths per year, could have been prevented and many could be cured.

Cigarette smoking causes lung cancer. It is not the only cause but it is the most important cause that we know about. In fact, the diagnosis in most cases of lung cancer ought to be *Chronic Tobacco Poisoning.* If death certificates were actually filled out this way, the public, the medical profession, and the governmental authorities might do more about what has become the greatest hazard to health and life in the United States today.

Most people say they would quit smoking if their physicians advised them to stop. Many would undoubtedly ignore such advice; but every physician should reevaluate his personal and professional attitudes and habits. If he is himself incurably addicted to cigarettes he should avoid smoking in the presence of his patients or anyone else who would respect his judgment and might follow the example he sets. He should question each patient about his use of tobacco and give each one good medical advice about this habit just as he would about the medical aspects of any other potential cause of disease and death.

Elimination of cigarette smoking would eventually reduce lung cancer to perhaps 25% of the present incidence. The control of this hazard to health will be accomplished slowly and, for many years to come, lung cancer will be a common problem. Until a more effective therapy is discovered we must concentrate on early diagnosis so that more of these cancers can be resected.

Many lung cancers cause abnormalities on the roentgenogram of the chest before symptoms develop. A common roentgenographic manifestation of asymptomatic lung cancer is an *uncalcified mass in the parenchyma* of the lung. Comparison of the film with old films is of great help in determining if the lesion is new or old. If it has been present for two years or longer without any change, it is reasonable to continue to observe it with serial chest films several times a year. Tomograms of the lesion may demonstrate calcification characteristic of a healed granuloma. Unless there is convincing evidence that the lesion is benign, it is wise to remove it, because the morbidity and mortality of this operation are not great. About half

*Humphrey, E. W.: Therapy for Carcinoma of the Lung. Minnesota Med. 53: 25, 1970.



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of the lesions requiring resection for diagnosis will be cancer; about half of these patients will be cured of their cancer by such an operation.

Another roentgenographic manifestation of asymptomatic bronchogenic carcinoma is *enlargement of the shadow of the root of the lung*. This shadow may appear to be within the upper limit of normal, but comparison with films made previously may reveal that there has been enlargement of the shadow. Therefore, all films with enlargement of one of the hilar shadows should be compared with older films. Thorough evaluation, including tomograms, fluoroscopy, bronchoscopy, and angiograms, may be needed to determine the cause of the abnormal shadow.

Routine examination of the sputum of healthy persons for cancer cells has been suggested as a case-finding technique because of the success of use of the Papanicolaou smear in the fight against cancer of the cervix. This is being investigated in several institutions at the present time. If these studies determine who should have the test and how often it should be repeated, routine examination of the sputum for cancer cells may become a valuable technique in our efforts to find lung cancer before it causes symptoms. Until more data are available, the routine chest x-ray film will remain the only generally available technique for finding asymptomatic lung cancer.

Unfortunately, most persons, even those who smoke, will not have routine chest x-ray examinations. Therefore their lung cancers will not be detected until they come to the physician with the first symptom, which may be shortness of breath, a cough of recent onset or worsening of a chronic cigarette cough, hemoptysis, wheezing, fever, or chest pain.

Because many cancers of the lung cause *obstructive pneumonitis* distal to the cancer, the possibility of cancer should be considered in every patient with pneumonia. No patient with pneumonia should be considered cured until a chest x-ray examination reveals complete clearing of the pneumonia without any residual abnormality. If the pneumonia does not clear promptly, the patient should have a bronchoscopic examination to detect any bronchial obstructing lesion that might account for the persistence of the pneumonia.

As soon as a diagnosis of lung cancer has been made, whether presumptive or proved, surgical treatment must be considered immediately, because it offers the patient the only significant chance of cure. As Humphrey points out, adjuvant preoperative radiation therapy is not beneficial and the various alternatives to surgery are not very effective.

Perhaps a more effective treatment for lung cancer will become available during the next decade. In the meantime, all physicians should rededicate themselves to the prevention of this form of cancer and to the prompt diagnosis and treatment of it when it does occur.

David T. Carr, M.D.
Rochester, Minnesota

Caution in Use of Chloramphenicol

Aplastic anemia remains the most serious among drug-induced blood dyscrasias because of its grave prognosis and unsatisfactory treatment. After a new drug becomes available for clinical use, it usually takes a long time before recognition of a causal relationship to marrow aplasia. The article by Mork et al.,* "Hematologic Toxicity of Chloramphenicol," in the October issue serves as a pointed reminder to physicians that this agent may produce irremediable bone-marrow damage. In at least some patients, even careful monitoring of peripheral blood counts is of no avail in preventing these disastrous effects. Although the incidence of marrow damage in patients receiving this antibiotic is low, the majority of affected patients do not recover. There is no justification for the use of this drug in relatively minor infections; and in life-threatening infections, other antibiotics with lesser toxicity can usually be used instead.

Joseph M. Kiely, M.D.
Rochester, Minnesota

*Mork, J. N., Thalhuber, W. H., and Swaim, W. R.: Hematologic Toxicity of Chloramphenicol. Minnesota Med 52: 1619, 1969.

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Hemolytic Anemia after Cardiac Surgery

VALVULAR HEART DISEASE, both treated and untreated, has been recognized as an important cause of increased red cell destruction and occasionally of resultant anemia. The report in the current issue of two cases of hemolysis associated with intracardiac prostheses again points out the occurrence of clinically significant hemolysis following operations on the aortic valve. In most cases the mechanism of red cell damage appears to be mechanical injury to the red cells due either to disturbed dynamic flow or perhaps to the direct action of the ball valve on the erythrocytes. In either event, the most important diagnostic clue is a morphologic result of this mechanical damage. Careful examination of the peripheral blood smear of patients with this type of hemolysis reveals the presence of schistocytes, burr cells, helmet cells and other euphonious distortions of the normal biconcave discs. Although more sophisticated tests may be necessary in order to adequately document the hemolysis, it should be emphasized that by far the most useful laboratory test is simple examination of the peripheral blood smear.

Since hemolysis of this type is predominantly intravascular, other confirmatory diagnostic tests can be done which demonstrate the presence of this type of hemolysis. Such tests include a disappearance of circulating haptoglobin, an increase in methemoglobin level, as well as an increase in plasma hemoglobin. In addition, significant amounts of urinary hemosiderin may appear. The search for urinary hemosiderin must be persistent; it may be necessary to examine multiple specimens of urine before a positive preparation is encountered. Also one may suspect the presence of hemolysis by other less specific tests including a falling hemoglobin in the absence of bleeding and a rise in the reticulocyte count.

There have been suggestions that some of the cases of hemolysis following cardiac surgery may be on an auto-immune basis. It has been found by some investigators including, for example, Polesky, that many patients both before and after cardiac surgery have a positive antiglobulin test (Coombs' test); but in most of the series reported there has been little evidence that the positive antiglobulin test indicated that there was an auto-antibody on the red cell causing hemolysis. It is well known that there are multiple causes for positive antiglobulin tests including previous blood transfusions, drugs and viruses. Thus the total reported experience does not suggest that hemolytic anemia occurs on an immunologic basis in significant numbers.

Shafer et al.* have emphasized conservative management of their patients. It does appear that the increased cardiac work due to anemia may well be better tolerated than the increased cardiac work which results from diseased valves. However, these patients obviously require very careful followups since, if their hemolysis becomes an increasing problem, reoperation may be the only effective means of treatment.

F. Bruce Lewis, M.D.
Minneapolis, Minnesota

*Shafer, Rex B. and Swaim, William R.: Hemolysis Associated with Intracardiac Prostheses. Minnesota Med. 52:1727, 1969.

Candidiasis

CERTAIN FORMS of candidiasis (oral thrush, vaginitis, and intertrigo) are familiar to most clinicians. Candida albicans is the yeast-like fungus most commonly found in candidiasis. Interestingly, Candida albicans is only a feeble pathogen and a normal saprophyte found in the gastrointestinal tract of many persons. The reason a patient develops candidiasis involves an underlying defect in the host rather than increased virulence of the organism. Although at

*Hermans, P. E.; Ritts, R. E., Jr.: Chronic Mucocutaneous Candidiasis. Minnesota Med. 53:75, 1970.

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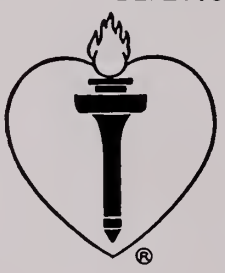
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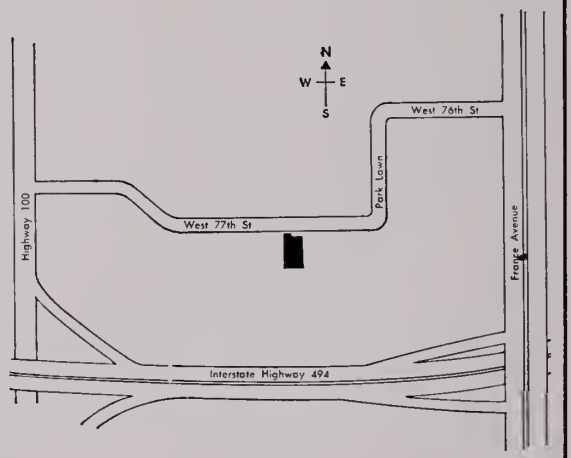
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times the host defect can be covert, many patients with acute candidiasis have an obvious local or systemic underlying pathologic condition which may predispose them to proliferation of the organism. Frequent maceration of hands in bartenders and dishwashers can predispose to interdigital candidiasis known as "erosio interdigitalis blastomycetica." Systemic medications and underlying conditions associated with acute candidiasis include broad-spectrum antibiotics, corticosteroids, immunosuppressive agents, pregnancy, infancy, debility, blood dyscrasias, lymphoproliferative diseases, metabolic and endocrine imbalances.[1]

Further information about defective host resistance in candidiasis is provided by Hermans and Ritts' article on chronic mucocutaneous candidiasis found in the January issue. Chronic mucocutaneous candidiasis is medically important but an infrequent resistant skin and mucous-membrane form that usually occurs in children. Hermans and Ritts have reviewed the clinical, endocrinologic and immunologic aspects of this form of candidiasis. Endocrinopathies associated with this type of candidiasis include hypoparathyroidism and hypoadrenalism. Of equal importance is the association of nonendocrine chronic mucocutaneous candidiasis with types of immunologic deficiency. As Hermans and Ritts have stated, the major immunologic abnormality in nonendocrine chronic mucocutaneous candidiasis is defective delayed-type hypersensitivity occurring as an isolated defect or as a part of one of the syndromes of thymic dysplasia (i.e., Swiss-type agammaglobulinemia).

Additional supporting evidence for a defective immunologic state in patients with chronic candidiasis is provided by two recent studies. Chilgren et al.[2] reported in-vivo cutaneous anergy and in-vitro reactivity of the cultured lymphocytes in patients with nonendocrine mucocutaneous candidiasis. Chilgren postulated that some patients with this form of candidiasis may have either a missing or inhibited mediator or chemotactic factor resulting in a defective efferent limb of the delayed-type of hypersensitivity. Canales et al.[3] reported the study of a patient with chronic mucocutaneous candidiasis having defective in-vivo and in-vitro delayed-type hypersensitivity which could be transferred by the patient's serum. Canales postulated that a serum factor may be present in their case which inhibited the proliferative responses of the small lymphocytes and impaired delayed hypersensitivity.

Harry Irving Katz, M.D.*
Minneapolis, Minnesota

*Clinical Assistant Professor, Department of Dermatology, University of Minnesota.

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3. Canales, L., Meddlemas, R. O., III, Louro, J. M., and South, M. A.: Immunological Observations in Chronic Mucocutaneous Candidiasis, Lancet 2:567, 1969.

She Won!

At the turn of the century the family doctor seriously inspected the tongue and examined the urine for sugar and albumin. The physician had just begun to study the blood as to appearance or chemistry. The common sore throat was painted with iodine. Arnica was an eclectic remedy; the eclectics believed there was an herb for every disease, and the eclectics were strong in Indianapolis. Once I cut my finger, and my mother chased me a mile and a half, trying to put on some arnica, which I hated because it burned. She succeeded.*

*Morris Fishbein, M.D., An Autobiography, 1969.

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Quality

"Quality, or whatever our term for what is good and valuable of its kind, is the chief element in almost all aesthetic appraisal; if not the whole, then certainly the heart, of criticism. What is good and valuable will seldom, of course, be flawless; but what it lacks, or in what ways it is limited, will neither disfigure nor discredit it, and in every age we feel the need to search it out."

Quality: Its Image in the Arts
Louis Kronenberger, Editor
Atheneum, New York, 1969

THE WINNERS of MINNESOTA MEDICINE'S 1969 Writing Awards are:

First Prize—Jesse E. Edwards, M.D.: Treatment of Coronary Disease: Pathologic Limitations, pages 1587-1596, October, 1969

Second Prize—William B. Kannel, M.D., William P. Castelli, M.D., and Patricia M. McNamara: Serum Lipid Fractions and Risk of Coronary Heart Disease, pages 1225-1230, August, 1969

and

LeRoy W. Matthews, M.D. and Carl F. Doershuk, M.D.: Management-Comprehensive Treatment of Cystic Fibrosis, pages 1506-1514, September, 1969.

Why these papers? Why did we, the Board of Editors of MINNESOTA MEDICINE consider them to be of such quality to merit the awards? I cannot answer collectively for the Board about these papers, but I have a few ideas about quality in medical writing in general.

The first idea concerns science, the second aesthetics.

You are acquainted, of course, with the first —hypothesis, experiment, confirmation in your head; then introduction, methods, results, and discussion on paper. It is something you can count on—objective, measurable, controlled, and controllable. You have come to expect this approach in original medical papers that seek to make valid scientific points.

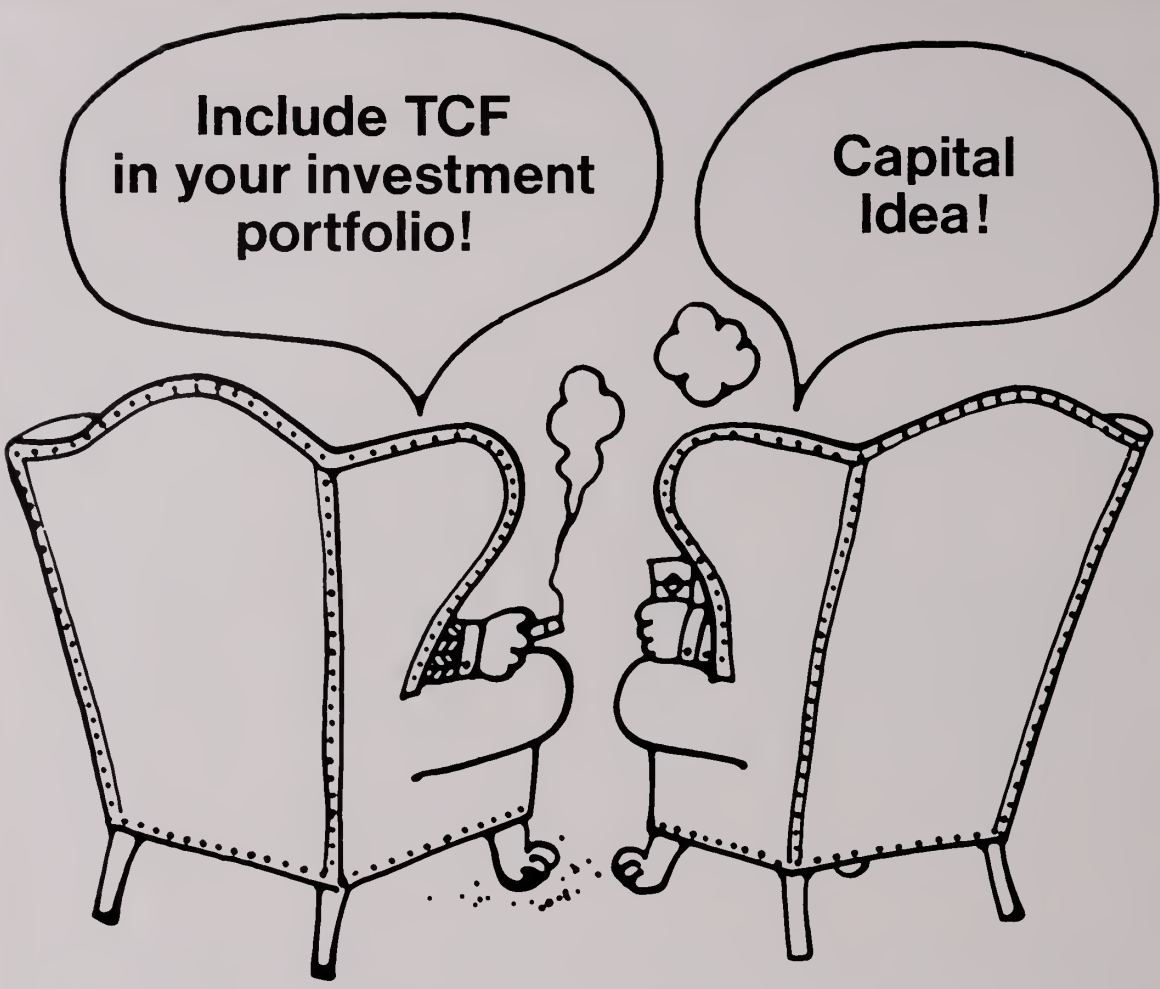
Needless to say, the selected papers meet the scientific criteria I have mentioned. The authors have broad scientific experience: Edwards with thousands of hearts that have passed before his eyes and through his hands; Kannel and his group with innumerable serum cholesterol, phospholipids, beta and pre-beta-lipoprotein measurements on 5,127 citizens of Framingham over a 14-year span; and Matthews and Doershuk with 404 children with cystic fibrosis followed the past 12 years. These articles have scientific merit, and we are proud that the authors chose to place their printed work in MINNESOTA MEDICINE.

The scientific method matters in quality medical writing, but in itself does not make an article readable. A scientific paper may be well designed, scientifically sound and grammatically impeccable. It may even pass through all editorial filters. Yet it sells flat, more dead than read.

I first became aware of the deadening effect of most scientific prose as a medical student. Try as I would, I could not understand the material, even when it excited me. At that stage of learning, I thought my reach exceeded my grasp. But no longer. Now that I have had some editorial experience, I realize that most articles are just badly written.

The problem, as I see it, is that physicians do not write as they think and feel. You do not write well unless you write as you perceive the world, through your eyes, your ears and your other senses, particularly your human sense. Every medical writer, like every Minnesota farmer, has to have a sense of humus—a sensitivity in presenting facts and ideas so they will take root, and being able to transplant these facts and ideas from his head to his readers is where aesthetic qualities count. Aesthetic simply means "received by the senses," and if you are writing to be read, you had best pay attention to your reader's senses.

Quality writing is partly a matter of the eye. Do not offend the reader's eye with a ponderous first paragraph, then completely blur his vision with huge blocks of print. Blepharo-



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spasm, vertical nystagmus and cerebral shutdown may ensue. Make your paper easy for him to follow with short opener, subheadings and short paragraphs composed of short sentences. Remember, if you write as you talk, in declarative sentences without flourishes, you will find all of this comes naturally for it is the simple declarative sentence which remains the architectural triumph of the English language.

And of the ear. When you're writing, remember someone out there may be listening. Better yet, pretend he is your friend, looking over your shoulder and asking questions. What do you mean by that sentence? Are you telling it the way you see it? Or if you cannot imagine him nearby, read it aloud to yourself. You will be surprised how many useless adjectives, awkward transitions, incomprehensive statements, and sheer verbiage you can spot (and cull).

There is also the matter of the meshing of minds—yours and your readers. What you compose in heat will sound flawless at first writing. But let it cool in a drawer for a week, and you will be able to look at it as a reader would. Then you will see clearly that which offends you—and him. And you will be ready for the final step—sifting the quality from the quantity.

What all this boils down to is taking time to please the reader—giving him the facts but anticipating his needs and wants without jarring his sensibilities.

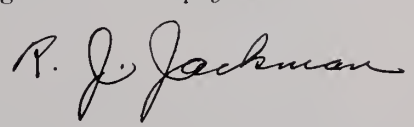
Richard L. Reece, M.D.
Minneapolis, Minnesota

President's Letter

(Continued from Page 603)

physicians' bills and 12 million bills for institutional services each year. Since Medicare began almost four years ago, only two physicians have been convicted of fraud in matters involved in that system. During that time, 2,500 cases have been investigated by the Social Security Administration. Commissioner Ball said, further, that it is clear from results of official investigation that the number of attempts at fraud or abuse is very small. In about half the cases investigated by the Social Security Administration difficulties were engendered by clerical errors, misunderstandings or honest mistakes made by physicians on health services dealing with a new and unfamiliar, cumbersome system. As of a few weeks ago, 13 other cases had been referred to the Department of Justice for criminal prosecution for fraud. Five other cases had been referred with recommendation that civil proceedings be started to compel return of funds. He said that data concerning possibly 25 other cases of fraud are being studied.

On a percentage basis, considerably less than 0.1 of 1% of those who provide health services were found to be dishonest. The lay press, which is always attracted by the bizarre and the unusual, ignores the extremely low proportion of fraudulence among those who receive government money for the rendering of medical care, but blows up into headlines the occasional instance of fraud in such a manner as to impugn the integrity of all physicians. Why not face reality and tell it as it is? Why is it not possible for all concerned parties to work together for the best interests of all, instead of trying to find a *scapegoat?*



Raymond J. Jackman, M.D., President,
Minnesota State Medical Association

We Wonder!

Why did Nature create man? Was it to show that she is big enough to make mistakes; or was it pure ignorance?—Holbrook Jackson



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The Editor's Soliloquy

Your Abbreviation I.Q.

Your Editor, who must review all manuscripts before publication, is sometimes taxed. Almost every author preparing a manuscript uses his own favorite abbreviations and there is no question in his mind about their collocations, though he may not be familiar with the list of abbreviations that some other author uses in his special and exclusive sphere of interest.

To give an oversimplified example: If on the first page of a long monograph you meet up with (axiobuccocervical) ABC or axiobuccogingival (ABG) or axiobuccolingual (ABL), does ABC or ABG or ABL always ring a clear bell of recognition when you are confronted with it thereafter in the same monograph? Or do you ask yourself: Now what did ABC or ABG or ABL mean; and do you glance back to page 1—only to have the said abbreviation play perverse hide-and-seek with your roving eye?

How about the twins: TKD and TKG; the triplets: s.v., s.v.r., s.v.t.; the quadruplets: CA, C.A., CCAT, CaCC? Who could be instantly and absolutely sure of his ground on: dg., o.s., Emp., M.I.O., N.A.D., F.vs., PcB, Ejusd., Sig.n.pro.?

Though the reading time may be considerably shortened when abbreviations are used, the comprehension time on random selections is considerably lengthened. The following extract from a recently submitted manuscript is a not too atypical example:

The initial cbc, C X-ray, EKG, ur & bl chem were neg. V.D.R.L., heterophile, L E prep and cold a. were neg. Throat cult grew out a strep; conj fl cult grew out Staph. C R and Cl T were N. U D revealed N C. H P I, CC, Ac & C S were X.

How did you come out?* I flunked it!

Carl O. Rice, M.D.

*For the answers see Page 648.

You May Be Right

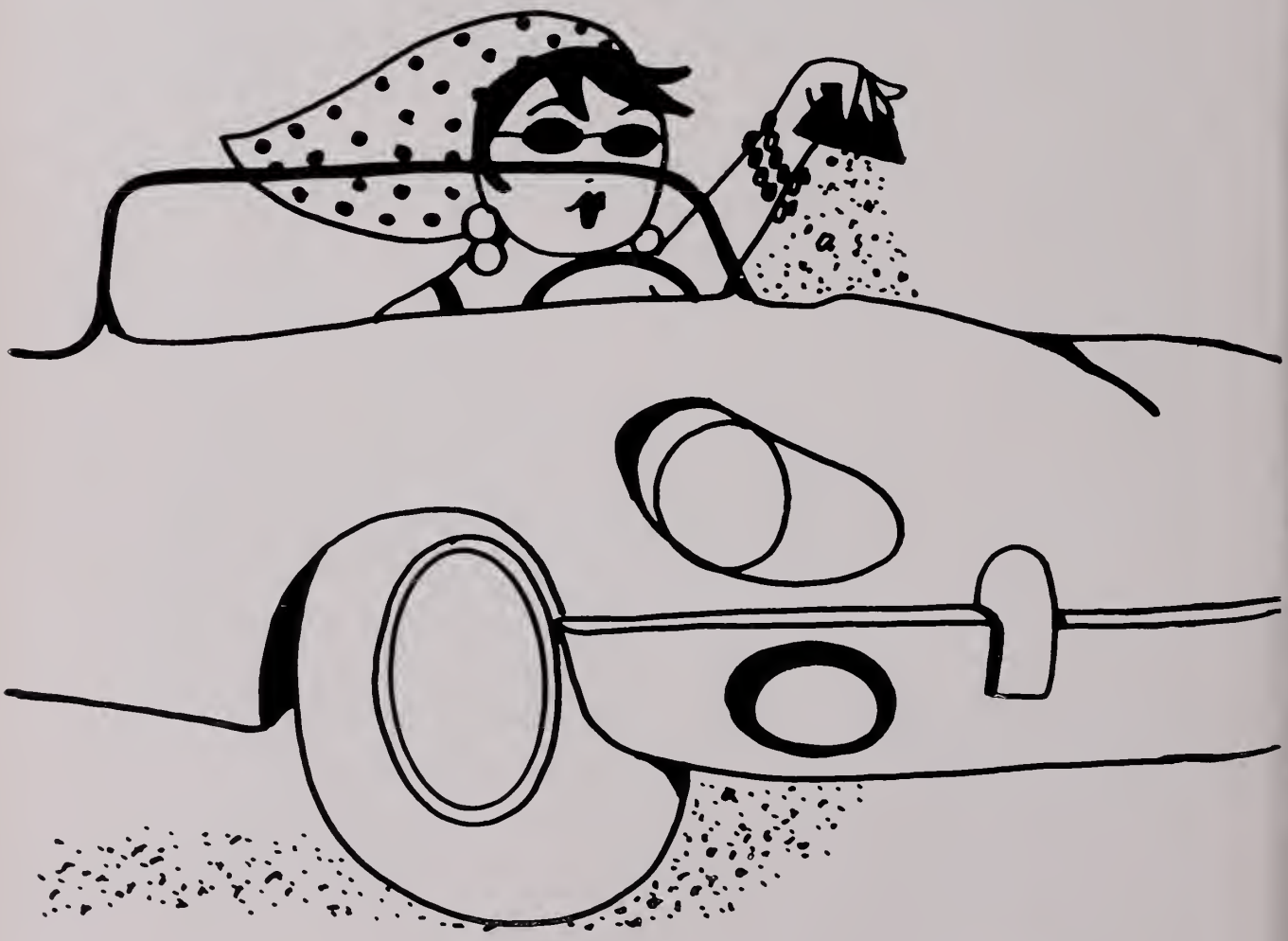
I should like to agree with the Editor that abbreviations have been a massive headache for me. In addition to having Webster's Unabridged Dictionary and Dorland's Medical Dictionary it is almost mandatory that the Medical Abbreviations Dictionary must be at hand in order to interpret many of the modern medical manuscripts. Webster's Unabridged Dictionary is not comprehensive and Dorland's is both incomplete and occasionally ambiguous. As you doubtless realize, periods too are important. For example, Ca, CA, and ca mean different things to a total of at least 15 completely separate items. For a writer to leave it to the context to establish the meaning of an abbreviation constitutes lazy and sloppy mentation. Let the reader guess, eh? At the risk of being considered a precisionist, I claim that in some fields there are no gray areas. I have no antipathy to foreign languages, the Latin terms, the Greek phrases, or French idioms, as these may lend status and prestige to the polymathic; curiosity and stimulation to the literate, and mysticism to the unlettered; but why must we confound one another with our individually concocted abridgments? Let's all get back to the uncondensed English language—with a minimum of ambiguous abbreviations and obscure acronyms. E.R.

OLD DOC HESS SAYS: A case report has its merits but it does not constitute a statistic. COR

MARY HAD AN ASHTRAY

by HENRY GIBSON

Mary had an ashtray
Full of ashes white as snow
And every time she drove her car
The tray would overflow.
She dumped it on the road one day
Which was against the rule.
The road is very ugly now
'Cause she was such a fool.



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PROSTATE GLAND

QUESTION: In the course of carrying out routine employment physical examinations I frequently encounter asymptomatic male patients over 50 years of age who have a solitary hard nodule of the prostate gland. In many of these cases the acid and alkaline phosphatase values are normal. Are such cases to be considered as carcinoma and treated accordingly? How would you advise managing such patients?

ANSWER: I consider all prostate glands containing indurated areas to be malignant until proved otherwise. The early malignant lesion may be confused with some benign conditions which cause areas of induration or nodules. Usually a cancerous nodule is not raised above the surface of the gland, and the consistency of the lesion, if compared with the surrounding tissue, offers a remarkable and sudden change. However, in the presence of such a hard nodule tissue examination is unquestionably indicated.

The acid phosphatase is frequently elevated in metastatic prostatic cancer but rarely elevated in cancer localized to the gland and almost never in benign prostatic hyperplasia. However, the alkaline phosphatase may be elevated in several different conditions: for example, in primary bone tumor, metastases to bone, Paget's disease, liver disease, etc.

Prostatic tissue for microscopic examination can be obtained by percutaneous needle biopsy, retropubic surgical biopsy, transurethral resection biopsy, transrectal needle or open surgical biopsy, or open surgical biopsy through a perineal approach. I favor the last approach as being the most accurate. It must be remembered that a negative needle biopsy does not necessarily indicate that cancer is not present. I prefer an open surgical perineal prostatic biopsy whenever the evidence is such that a radical prostatovesiculectomy is most probably indicated. If a frozen section reveals malignancy I then change the patient's position to permit a retropubic approach.

It must be understood that patients with prostatic carcinoma are in an age group which makes them susceptible to several different associated disease conditions which may markedly increase the operative risk; therefore, a general evaluation of the patient is of primary importance. I always consider the life expectancy for a patient in this category before a radical operative procedure is planned. It has been generally accepted that radical prostatectomy should not be carried out in patients older than seventy years. However, the

general physical condition of such patients should be thoroughly assessed before automatically excluding them from surgery on the basis of age alone. The status of the cardiovascular, pulmonary, and gastrointestinal systems as well as renal function deserve special attention. Intravenous urography should be done routinely. Roentgenography of the pelvic bones to detect metastatic lesions is an important preliminary study. Experience in the treatment of carcinoma of the prostate teaches that once neoplastic cells have spread out of the prostatic capsule the condition is no longer curable.

Rafael S. Misa, M.D.*
Montgomery, Alabama

*Chief of Urology, Veterans Administration Hospital, Montgomery, Alabama.

URINARY BLADDER CARCINOMA

QUESTION: What is the current role of chemotherapy in the treatment of carcinoma of the urinary bladder?

ANSWER: Chemotherapy in the treatment of carcinoma of the urinary bladder is still in a trial period. Conclusions drawn as to the efficacy of treatment using these agents must be weighed in the light of the limited experience which has been gained to date with their use.

The use of two parenteral drugs, 5-fluorouracil and citral, has been reported. Their effects have not been dramatic. Treatment of bladder tumors by instillation of thiotepa, actinomycin D, or 5-fluorouracil into the urinary bladder has been reported with encouraging results.

Best results have occurred in those cases treated with instillations of 60 mgm. of triethylenethiophosphoramide (thiotepa) dissolved in 30-60 ml. of normal saline. My personal experience with this drug, when used as described, is very encouraging although I have treated only a limited number of cases.

The Veterans Administration Surgical Adjuvant Group reported on a series of cases treated by continuous intra-arterial infusion of various drugs including methotrexate, methotrexate with citrovorum, 5-fluorouracil, 5-fluorodeoxyuridine, and thiotepa. Of six patients suitable for objective evaluation, three showed more than a 50% regression in the size of their tumors.

Rafael S. Misa, M.D.
Montgomery, Alabama

Answers to Your Abbreviation Score (from page 643)

Translated this means: "The initial hemogram, chest film, electrocardiogram, urine analysis and blood chemistry were negative. Tests for venereal disease, heterophile, lupus erythematosus, and cold agglutinins were negative. Throat cultures grew out alpha strep; conjunctival fluid cultures grew out Staphylococcus. Clot retraction and clotting time were negative. Urethral discharge revealed no culture. The history of present illness, current complaints, acute and convalescent status were unknown."

Every one of these abbreviations is familiar to those who use them, but not necessarily to all who read them—nor to the printer to whom their accurate transcription must be most vexatious. They are all included in a medical dictionary of abbreviations. If it is typewriter ribbon you're trying to save, let us know! —C.O.R.

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*An estimated 208,000 patients have received GARAMYCIN Injectable to date. The combined population of Duluth, Winona, and Bloomington is 205,500. (Estimated 1969 figures from The New York Times Encyclopedic Almanac 1970.)

See Clinical Considerations section on last page...

Mounting acceptance in the hospital...

Proven clinical effectiveness



Respiratory Infections

Outstanding results in serious gram-negative respiratory infections[1,2]

GARAMYCIN Injectable may prove successful where other antibiotics have failed.



Urinary Tract Infections

Strikingly effective in selected urinary tract infections[3]

With relatively low intramuscular doses, the promptly attained levels of GARAMYCIN achieved in the urine are considerably higher than the concentrations required for effectiveness against virtually all susceptible gram-negative pathogens. (Appropriate precautions are indicated in patients with impaired renal function; consult Package Insert for full details.)



Septicemia

May be lifesaving[4-6]

Numerous investigators have drawn attention to the value of GARAMYCIN Injectable in the treatment of gram-negative septicemias, often complicated by shock. Many hospital strains of *Serratia* are susceptible.[6]



Wounds and Burns

Response may be dramatic in wounds and burns complicated by sepsis[7]

The established efficacy of GARAMYCIN Injectable against *Pseudomonas*—as well as most other gram-negative pathogens—makes it an especially useful agent in the treatment of infected wounds and burns.

Important Precautionary Note Patients receiving treatment with GARAMYCIN Injectable (gentamicin sulfate injection) should be under close clinical observation because of the toxicity associated with the use of the drug. Ototoxicity, vestibular and auditory, can occur in patients, primarily those with preexisting renal damage, treated with GARAMYCIN Injectable for longer periods or with higher doses than recommended.

GARAMYCIN Injectable is potentially nephrotoxic, and this should be kept in mind when it is used in patients with preexisting renal damage.

This drug should be limited to the treatment of serious infections caused by susceptible gram-negative bacteria, with due regard for relative antibiotic toxicity. (See Clinical Considerations section.)

Mounting evidence in the laboratory...

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Over 95% gram-negative pathogens sensitive.*

No other antibiotic performed comparably *in vitro* against gram-negative pathogens.
In a nationwide culture audit of antibiotic sensitivity patterns, sensitivity reports from 106 hospitals, geographically representative by census tract and of varying sizes, were analyzed. During the three-month period, ***every*** gram-negative culture slip from ***every*** hospital was surveyed. The total number of cultures involved in the audit was 97,091. The total number of sensitivity determinations was 643,503.

Pathogens	Percentage of sensitive strains / Number of strains tested — Antibiotics*							
	Garamycin	Kanamycin	Cephalothin	Cephaloridine	Ampicillin	Colistimethate	Chloramphenicol	Tetracycline
Klebsiella pneumoniae	99.5% 962	84.7% 992	86.2% 995	76.1% 67	32.7% 1,020	96.3% 640	82.9% 1,028	77.1% 1,026
Aerobacter aerogenes	95.9% 2,739	86.1% 2,818	53.5% 2,985	58.8% 1,514	22.7% 3,066	88.6% 2,603	85.8% 3,071	67.8% 2,981
Klebsiella aerobacter group	98.8% 566	83.9% 547	66.1% 522	60.5% 276	28.0% 553	89.5% 560	86.2% 587	62.8% 433
Klebsiella, all others	92.7% 2,944	83.3% 3,186	77.4% 2,976	67.5% 627	13.5% 2,883	95.0% 2,105	81.6% 3,212	70.6% 3,063
Pseudomonas aeruginosa	91.6% 4,528	29.8% 4,460	6.6% 4,418	6.6% 1,279	6.0% 4,360	91.3% 3,852	26.9% 4,608	26.4% 4,404
Proteus, indole-positive	91.8% 1,031	85.8% 1,062	39.9% 981	54.1% 364	40.2% 1,042	10.3% 758	76.1% 1,096	42.1% 1,051
Proteus mirabilis, indole-negative	94.9% 3,272	90.1% 3,378	83.1% 3,290	77.5% 975	78.0% 3,274	8.8% 2,634	85.9% 3,469	26.8% 3,278
Proteus, unspecified	96.2% 1,335	85.8% 1,371	71.7% 1,434	70.0% 647	64.7% 1,435	11.2% 1,233	76.0% 1,421	22.4% 1,298
Escherichia coli and all other *Escherichias*	96.4% 12,557	91.4% 12,818	87.8% 12,686	88.8% 4,251	74.6% 12,899	95.4% 10,623	94.1% 13,086	70.0% 12,559
Paracolobactrum, all	93.4% 303	88.9% 325	62.0% 305	74.2% 62	43.8% 340	80.9% 215	87.1% 350	72.6% 340
Coliform bacteria	99.0% 593	91.2% 649	81.5% 637	66.7% 21	52.7% 624	95.6% 607	91.6% 678	76.1% 637
Totals	95.1% 30,830	80.5% 31,606	65.3% 31,229	68.1% 10,083	50.3% 31,496	75.8% 25,829	79.7% 32,606	56.5% 31,070
Gram-positive (included for consistency with Package Insert, not an approved indication)								
Staph—*S. aureus*, coagulase-positive	97.4% 1,548	88.8% 1,458	97.7% 2,050	98.7% 636	61.1% 1,559	20.4% 628	94.4% 2,123	83.7% 1,966
Staph—*S. aureus*, unspecified	99.3% 993	92.8% 902	98.1% 1,289	95.3% 213	45.8% 1,153	29.3% 116	96.4% 1,427	82.3% 1,360

*Adapted from a three-month, nationwide hospital audit by R. A. Gosselin and Co., Inc., Dedham, Massachusetts (mid-May to mid-August, 1969).[8]
Antibiotics with significant gram-negative spectra are included. Organisms are listed as reported by laboratory.
Sensitivity testing was done by the disc method, a generally reliable test in the hospital setting. It should be noted, however, that the results with GARAMYCIN were somewhat higher than the results reported where the tube dilution technique was used. (See Clinical Considerations section which follows.) The concentration of the GARAMYCIN disc was 10 mcg.
Whereas standard testing methods were used by all hospitals, it is acknowledged that in a survey of this kind considerations such as differences in methodology are possible sources of error. The comparative percentage-sensitivity results derived from a survey of this kind are, therefore, not absolute. One should keep in mind also that the proper selection of an antibiotic is based not only on susceptibility testing but on relative toxicity and other clinical considerations as well.
It is felt, nonetheless, that the broad scope of the survey and the extreme care in data collection and tabulation permit a conclusion that the results are *generally* representative of current nationwide antibiotic sensitivity patterns.

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brand of gentamicin sulfate injection

See Clinical Considerations section on last page...

Injectable Garamycin®

brand of gentamicin sulfate injection

Schering

ADULT DOSAGE GUIDELINES

See definitive prescribing information in Package Insert.

Patients with Normal Renal Function

Total Daily Dose (administered in two, three, or four divided doses)			
	Less Severe	**Resistant/ Moderately Severe**	**Serious/Life-Threatening**
Urinary Tract Infections (due to susceptible strains of gram-negative bacteria)†	0.8-1.2 mg./kg. for 7-10 days	Larger doses or additional antibacterial therapy should be considered in severe urinary tract infections or in resistant cases involving the renal parenchyma or anatomic anomaly.	up to 5 mg./kg.
Other Infections including bacteremia, infected surgical wounds, severe soft tissue infections, and respiratory tract infections (due to susceptible strains of gram-negative bacteria)	3 mg./kg. for 7-10 days		

†Alkalinization of the urine may be a useful therapeutic adjunct.

Patients with Impaired Renal Function

To minimize the risk of ototoxicity in patients with impaired kidney function, only the first dose should be that normally recommended. Each subsequent dose should be half or less of that recommended for patients with normal renal function, depending upon the degree of renal impairment.

In patients with renal failure who are undergoing 14-hour hemodialysis twice weekly, administration of 1 mg./kg. GARAMYCIN Injectable at the end of each dialysis period has been suggested.

Clinical Considerations

Indications: GARAMYCIN Injectable is clinically effective in infections due to susceptible strains of gram-negative bacteria, including *Pseudomonas aeruginosa,* and species of indole-positive and indole-negative *Proteus, Escherichia coli,* and *Klebsiella-Aerobacter.* Bacteriologic studies should be conducted to identify the causative organism and to determine its sensitivity to gentamicin sulfate. Sensitivity discs of the drug are available for this purpose. If the susceptibility tests indicate that the causative organism is resistant to gentamicin sulfate, other appropriate antibiotic therapy should be instituted.

IN VITRO INHIBITION OF CLINICALLY IMPORTANT BACTERIA BY GENTAMICIN SULFATE (TUBE DILUTION STUDIES)

BACTERIA	No. of Strains Tested	No. of Strains (%) Inhibited by: 4 mcg./cc. or less		8 mcg./cc. or less*		No. of *In Vitro* Studies
Staphylococcus aureus	1,210	1,200	(99%)	1,206	(99%)	11
Pseudomonas aeruginosa	885	771	(87%)	828	(93%)	16
Escherichia coli	836	736	(88%)	779	(93%)	11
Indole-positive and indole-negative *Proteus* species	477	210	(44%)	358	(75%)	12
Klebsiella-Aerobacter species	292	205	(70%)	231	(79%)	10

*Number of strains (%) of gram-negative bacteria inhibited by 10 mcg./cc. or less are as follows: *Pseudomonas aeruginosa,* 828 (93%); *Escherichia coli,* 792 (95%); *Proteus* species, 393 (82%); *Klebsiella-Aerobacter* species, 284 (97%). From same studies as above.
Source: Package Insert

This drug should be limited to the treatment of serious infections caused by gram-negative bacteria, particularly *Pseudomonas aeruginosa, Proteus* and other susceptible organisms, with due regard for relative antibiotic toxicity. Therefore, the drug should be considered for use against gram-negative: 1. Bacteremia; 2. Infected surgical wounds; 3. Severe soft tissue infections, including burns complicated by sepsis; 4. Respiratory tract infections; and 5. Selected cases of urinary tract infection.

Contraindications: GARAMYCIN Injectable is contraindicated in individuals with a history of hypersensitivity or toxic reactions to gentamicin.

Warnings: Patients receiving treatment with GARAMYCIN should be under close clinical observation because of the toxicity associated with the use of this drug. Ototoxicity, vestibular and auditory, can occur in patients, primarily those with pre-existing renal damage, treated with GARAMYCIN Injectable usually for longer periods or with higher doses than recommended.

GARAMYCIN Injectable is potentially nephrotoxic, and this should be kept in mind when it is used in patients with pre-existing renal impairment. Kidney function diminished by infection of the upper urinary tract may, however, improve during effective treatment with GARAMYCIN Injectable.

Concurrent administration of potentially ototoxic drugs such as streptomycin and kanamycin or of potentially nephrotoxic drugs such as polymyxin, colistin, and kanamycin with gentamicin sulfate has not been shown to afford any clinical advantages and, moreover may result in additive toxicity. Monitoring of vestibular, cochlear, and renal function will provide guidance for therapy in such cases.

Precautions: In patients with impaired renal function in whom serious infection develops, serum concentrations of the drug may rise, with consequently increased risk of ototoxicity. In these patients or in those in whom recommended dosage or duration of therapy must be exceeded as a life-saving measure, routine studies of kidney function should be performed when possible. These may be supplemented by evaluation of the vestibular and auditory function and measurement of serum concentration of the drug when feasible. Serum concentrations of gentamicin should be maintained below the range of 10-12 mcg./ml. to reduce risk of ototoxicity.

Ordinarily, treatment should not be given for more than 7 to 10 days or be repeated unless required for serious infection not responsive to other agents.

As with other antibiotics, treatment with GARAMYCIN Injectable may occasionally result in overgrowth of nonsensitive organisms. If superinfection occurs, appropriate therapy is indicated.

Safety for use in pregnancy or the potential for fetal ototoxicity or nephrotoxicity have not been established. Studies in pregnant animals have not revealed teratogenic or ototoxic effects in the fetus. GARAMYCIN Injectable should not be used in pregnant patients or in women of childbearing age unless its use is deemed advisable by the physician.

Adverse Reactions: The overall incidence of ototoxicity considered related to treatment with GARAMYCIN Injectable was 2.8 per cent (16 of 565 patients). Contributory factors (two or more factors were relevant to most patients) were as follows: 10 had azotemia, 10 received a total of 1 gram or more of the drug, 7 had recently received other potentially ototoxic antibiotics (streptomycin or kanamycin), and 5 were over 60 years of age. Six also had decreased high-tone hearing acuity, which returned to or toward normal in the 4 patients retested.

Analysis of BUN data indicated that 4 (2%) of 172 patients showed increases in BUN that were probably related to treatment with GARAMYCIN Injectable. Of 20 increases probably or possibly related to treatment, 7 were reversible, 9 occurred in terminal patients, and 4 had no follow-up.

Other adverse reactions associated with treatment were one instance each of urticaria, decreased hematocrit, and reversible depression of granulocytes with normal bone marrow. Other rarely reported and possibly treatment-related adverse reactions were anemia, increased reticulocyte count, rash, purpura, drug fever, hypotension, convulsions, twitching, salivation, nausea, vomiting, increased transaminase activity (SGOT or SGPT), increased serum bilirubin, decreased serum calcium, and joint pain.

Packaging: GARAMYCIN Injectable, 40 mg./cc., 2-cc. multiple-dose vials, for intramuscular administration.

References: (1) Brayton, R. G., and Louria, D. B.: Gentamicin in gram-negative urinary and pulmonary infections, Arch. Int. Med. *114*:205, 1964.* (2) Louria, D. B.; Young, L.; Armstrong, D., and Smith, J. K.: Gentamicin in the treatment of pulmonary infections, J. Infect. Dis. *119*:483, 1969. (3) Cox, C. E.: Gentamicin, a new aminoglycoside antibiotic: Clinical and laboratory studies in urinary tract infections, J. Infect. Dis. *119*:486, 1969. (4) Groll, E.: Clinical experience with gentamicin, data from 12 German clinics, in Gentamicin: First International Symposium, Paris, January 1967, Lucerne, Essex Chemie AG, pp. 121-128.* (5) Jackson, G. G.: Laboratory and clinical investigation of gentamicin, *ibid.*, pp. 62-74. (6) Medeiros, A. E.: Discussion, J. Infect. Dis. *119*:533, 1969. (7) Polk, H.: Discussion, J. Infect. Dis. *119*:529, 1969. (8) Three-month, nationwide hospital audit by R. A. Gosselin and Co., Inc., Dedham, Massachusetts (mid-May to mid-August, 1969).

*Dosage in this investigational study was less than now recommended in Package Insert.

For more complete prescribing details, consult package insert or Physicians' Desk Reference. Schering literature is also available from your Schering Representative or Medical Services Department, Schering Corporation, Union, New Jersey 07083.

AHFS CATEGORY 8:12.28 5-029

The Viewing Box

Distal Clavicular Resorption

This 54-year-old female was admitted to the hospital with epigastric pain and hematemesis. An upper GI series revealed a duodenal ulcer. A chest film was obtained (Figure 1). Look closely at the distal clavicles. You will note that there is resorption of the clavicular bone and widening of the acromio-clavicular joints (Figures 1 and 2). What was the patient's underlying disease?

What is your diagnosis? (See next page.)



Fig. 1—Routine roentgenogram of chest.

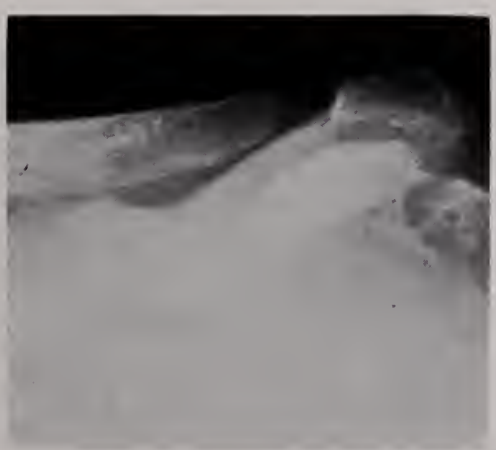


Fig. 2—Left acromio-clavicular joint.

If you said rheumatoid arthritis, you were correct. The patient had had rheumatoid arthritis for several years and had been taking cortisone, indocin, and aspirin. Very likely her GI bleeding was secondary to the arthritis therapy.

Periodic reports in the literature have described destructive changes at the outer end of the clavicles in association with rheumatoid arthritis. The pathology is not completely clear but it is felt that the erosion is similar to loss of bone in mutilating arthritis and that there is a replacement of the involved bone, articular cartilage and synovial membrane by fat or fibrous tissue. The x-ray reveals a striking loss of bone at the acromial end of each clavicle. The outer clavicle may appear tapered or beaked with the changes more marked inferiorly. Articular cystic change may occur at the A-C joint, more pronounced on the clavicular side. Widening of the A-C joint occurs up to 15 mm, compared to a normal of 2-5 mm. The arthritic process may also narrow the A-C joints and progress on to sclerosis and bony ankylosis.

In general, resorption of bone may be produced by vascular, neuropathic, inflammatory or metabolic conditions.[1] Local factors such as trauma or thermal injuries may be causative.

Alpert et al.[2] have listed an excellent differential diagnosis of distal clavicular resorption which includes: hyperparathyroidism, scleroderma, osteogenesis imperfecta, tuberculosis, A-C dislocation, surgical resection, post-traumatic osteolysis, degenerative arthritis and neoplasm. Erosions of the clavicles have been described in patients with severe psoriatic arthritis, and unilateral A-C arthritis has been observed in a patient with long standing Marie-Strumpell arthritis. Erosions are also encountered in reticulohistiocytoma.[3] This disease, also known as lipoid dermatoarthritis, is a grave condition of unknown etiology which affects the skin, bones and joints.

In addition to similar clavicular changes frequently seen in hyperparathyroidism, subperiosteal cortical resorption of phalanges, demineralization of the skull and loss of the lamina dura will usually be observed. Loss of clavicular bone is rare in scleroderma and the patient will usually demonstrate Raynaud's phenomenon, skin changes, dysphagia and ulceration of the finger tips. One will observe a slender tapered clavicle in osteogenesis imperfecta, but these individuals should have hypermobile articulations, bowing of the long bones and fresh fractures. A painful soft tissue mass and draining sinus are observed in tuberculosis of a single A-C joint. Other inflammatory lesions that may involve the A-C joints, such as pyogenic osteomyelitis, mycotic infection, gumma and eosinophilic granuloma, are also unilateral. With a history of trauma or surgery one should have no difficulty in distinguishing A-C dislocation and surgical resection from rheumatoid arthritis. The bone destruction in post-traumatic osteolysis is usually unilateral and may progress on to involve the ribs and scapula. Degenerative arthritis demonstrates sclerosis and osteophyte formation. Primary and secondary neoplasms of the clavicle are rare and would usually be unilateral.

Clavicular resorptive changes in rheumatoid arthritis will be observed bilaterally. The many associated bone and joint abnormalities seen in rheumatoid arthritis will easily distinguish this disease from others in the above differential diagnosis.

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References may be secured from the author or the reprints.

Life is a measure to be filled—not a cup to be drained.—Fifth Wheel

Neurological Grand Rounds

Trigeminal Neuralgia

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THE PAINFUL AFFLICTION of the face termed trigeminal neuralgia, trifacial neuralgia, or tic douloureux was first described by Nicolus Andre in 1756. Fothergill, in 1773, described the clinical features of this condition and his name remains linked to this disease. Although the characteristic pain has been clearly identified, both its cause and its treatment remain obscure. It was not until the work of Magendie and Bell that the trigeminal nerve rather than the facial nerve was recognized as the involved structure. Previously the facial nerve had been sectioned in vain efforts to treat the condition.

The disorder is characterized by sharp, sudden, lancinating pains in the distribution of one or more branches of the trigeminal nerve. The majority of patients with this disease are over 50 years of age and women are more often affected than men. Children are also said to be occasionally affected. Trigeminal neuralgia is usually limited to one side of the face, although in one to three percent, the opposite side may be affected later. Attacks never occur on both sides simultaneously.

Anatomy

The Fifth Nerve

The fifth nerve is the largest of the cranial nerves. It is the major cutaneous sensory nerve of the face, the sensory nerve to the mucous membranes and other internal structures of the head, and the motor nerve of the muscles of mastication. It has two roots, the sensory being much larger than the motor.

The Ganglion

The trigeminal ganglion lies in a pocket of dura mater which occupies the trigeminal impression near the apex of the petrous portion of the temporal bone. The peripheral fibers from the ganglion are collected into three large divisions: (1) the ophthalmic, (2) the maxillary, and (3) the mandibular nerves. The ophthalmic and maxillary nerves remain sensory, but the mandibular becomes mixed, being joined by the motor root just outside the skull. The ophthalmic nerve, or first division of the trigeminal, leaves the anterior superior part of the ganglion, and enters the orbit through the superior orbital fissure. It is a sensory nerve supplying the bulb of the eye, conjunctiva, lacrimal gland, part of the mucous membranes of the nose and paranasal sinuses, and the skin of the forehead, eyelids, and nose.

The Maxillary Nerve

The maxillary nerve, or second division of the ganglion, is intermediate in position and size between the other two nerves and, like the ophthalmic,

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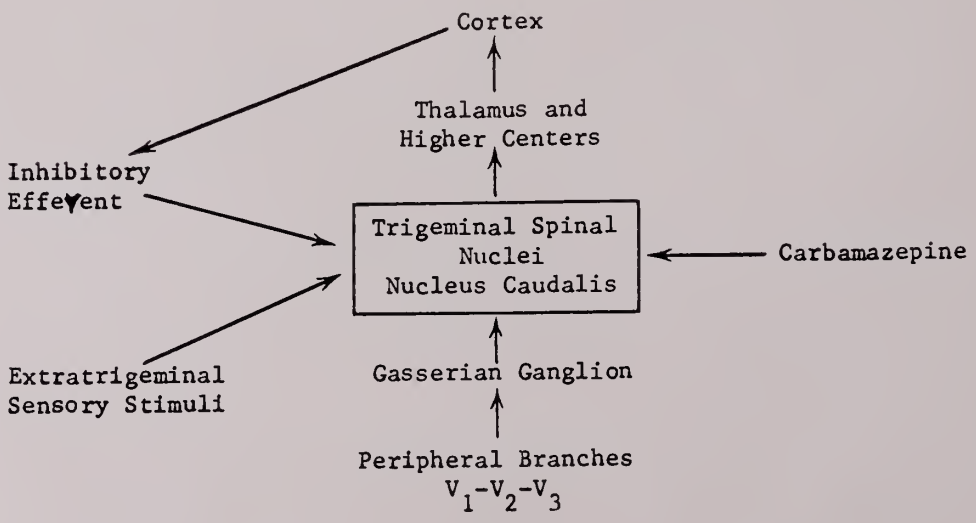
is entirely sensory. It supplies the skin of the middle portion of the face, lower eyelid, side of the nose, and upper lip; the mucous membrane of the nasopharynx, maxillary sinus, soft palate, tonsil and roof of the mouth, the upper gums and teeth.

The mandibular nerve, or third and largest division of the trigeminal, is mixed and has two roots. The sensory fibers supply the skin of the temporal region, ear, external meatus, cheek, lower lip, and lower part of the face; the mucous membrane of the cheek, tongue and mastoid air cells; the lower teeth and gums; the mandible and temporomandibular joint; and part of the dura mater and skull. The motor fibers supply the muscles of mastication, the mylohyoideus and anterior belly of the digastricus, and the tensors tympani and veli palatini. The two roots leave the middle cranial fossa through the foramen ovale, and unite just outside the skull. From there the fibers pass to the areas of the face already mentioned.

Etiology

The etiology of trigeminal neuralgia is unknown. The trigeminal (gasserian) ganglion and its surroundings have been examined histologically and no uniform change has been discovered. The relationship of arteriosclerosis and trigeminal neuralgia is not constant. A passive relationship between the pain and dental caries has also been extensively explored, but removal of the teeth is more often than not of no avail. The fact that relief of pain is obtained from cutting peripheral nerve fibers by blocking them or cutting the roots indicates only that the individual attacks of pain are precipitated by peripheral stimuli and means little so far as the etiology of the condition is concerned. Multiple sclerosis may produce trigeminal neuralgia in relatively young individuals. In the few instances in which autopsies have been performed on such patients, patches of demyelination have been

Possible Mechanism of Tic Douloureaux



Figure

found at the point where the fifth nerve enters the pons. An irritative lesion, such as a hemorrhage or tumor about the gasserian (trigeminal) ganglion, may evoke neuralgia and facial pain which is distinguished only with difficulty from that of tic douloureux.

Symptoms and Signs

Any of the divisions of the fifth nerve may be involved, alone or in combination. Fortunately, the ophthalmic division is far less frequently involved than the others, and only very occasionally alone. The first symptoms may be interpreted by the patient as originating from his teeth, so that, as mentioned previously, dental caries may be suspected. A series of paroxysms of facial pain may be followed by a long pain-free interval. The intermissions between the paroxysms may extend from weeks to years. Generally, with each succeeding attack, the seizures become more frequent, severe and intolerable.

The Trigger Point

The pain usually begins at a fairly constant point, called the trigger point, stimulation of which sets off an attack of pain. Commonly, the points are on the margin of the upper or lower lip, or along the side of the nose. Less commonly, the pain may originate in the gum, near a tooth, or even on the side of the tongue. The trigger zone for the ophthalmic division is on the forehead over the eyebrow. Gentle stroking of a trigger point will rapidly induce a burst of pain. For that reason, patients are very careful not to touch the sensitive spot, or permit others to do so. From the point of origin, the pain shoots into other parts of that division or into the neighboring division of the fifth nerve. Its character is variable, but most always severe. It is described as sharp and shooting, like red-hot needles, like an electric shock, or like knives being thrust into the face.

During an attack, the patient usually ceases all conversation. His face expresses his terrific suffering as he grimaces and tries to remain immobile during the attack. Some individuals rub or press their hands against their face. After a few moments, the pain spontaneously ceases and the patient shows profound relief. Movement of the face, jaws and tongue in talking and eating can also precipitate an attack. Accordingly, these patients tend to hold the affected side of the face more or less continuously immobile, and some of them become seriously emaciated and dehydrated because they refuse to eat or drink. Washing or shaving is often very painful, and a few patients reach a stage in which their faces are deeply encrusted with dirt on the affected side. However, periods of remission are fairly common and, on occasion, the pain may disappear spontaneously for several months or years.

Physiology

Current neurophysiological research has demonstrated that the nucleus caudalis of the trigeminal nuclear complex relays most of the trigeminal input to specific loci in the midbrain. It has been shown in the cat that strychnine applied to the nucleus caudalis will induce facial overreaction to tactile stimuli. A possible explanation of tic douloureux may thus be offered based on this information. In brief, the disease may be manifested by a state of abnormal reactivity of the spinal trigeminal nuclei. Theoretically, carbamazepine will diminish the reactivity of the trigeminal nuclei, decreasing their

synaptic activity and thereby ameliorate the disease.

Medical Treatment

A good medical regimen should be rigidly and stringently attempted before surgery is tried. Trichlorethylene was one of the earlier treatments used in some cases wherein the pain was not yet severe or when the general condition of the patient precluded more radical measures. Trichlorethylene is a commercial solvent used in the removal of oil and grease from motor parts. Inhaled in doses of twenty to thirty drops several times daily, it gave relief to some patients. However, it is not specific for the facial pain but selectively affects all pain sense. To relieve severe and unremitting pain a general analgesic agent may have to be used, e.g., Talwin, Leritine or, in extremely severe cases, Demerol.

Anticonvulsants

Anticonvulsants have been the treatment of choice in recent years. Dilantin is the preferred drug. Dosages range from 100 mgm. three times daily to more toxic levels, up to 500 mgm. per day. This is a particularly effective regimen and may produce relief for the patient for long periods. Above these levels, unpleasant symptoms, such as dizziness, muscular incoordination, gastrointestinal disturbances, severe swelling of the gums, or loss of weight, may appear. Incoordination is the most frequent complication.

Iminostilbene

A new drug has recently appeared on the market called "carbamazepine" or Tegretol. It was first described in the European literature of the early 1960s and is an iminostilbene, related to the imipramine group of drugs, *not* to the hydantoin.

Dalessia of the Scripps Clinic and Research Foundation devised a pilot study with 25 patients (seven male; 18 female), each patient having had operative procedures on the trigeminal nerve previously with disappointing results. They were given 200 mgm. of Tegretol three times a day. In 48 hours, 18 out of 25, or 72%, reported excellent results with regard to pain relief, a result which compares well with the European data. Once the dosage and therapeutic efficacy of the agent were determined, a double-blind study was devised. Twenty patients were tested and all had good relief of pain when taking the Tegretol rather than placebo. Recommended doses for carbamazepine are: 100 mgm. (½ tablet) twice on the first day, always with meals. Thereafter, the dose should be gradually increased in 100 mgm. (½ tablet) increments every 12 hours until freedom from pain is achieved. The dose necessary may vary from 200 mgm. to 1200 mgm. per 24 hours. With regard to maintenance, initial control of pain can be maintained in most patients with a dose of 400 mgm. daily. However, some cases may be maintained on as little as 200 mgm. per day, while others may require 1200 mgm. per day.

At high levels, this drug may have *side effects* which include: aplastic anemia, agranulocytosis, thrombocytopenia and transitory leukopenia; in fact, deaths have been reported following the use of this drug when high dosages have been used. It is therefore essential to detect serious bone marrow injury early. Complete blood and platelet counts should be done at frequent intervals. Liver damage has also been reported. Less serious complications include dizzi-

ness, drowsiness, unsteadiness, nausea, and vomiting.

Surgical Treatment

If the medical regimen fails, semi-permanent and permanent control of the facial pain may be achieved by surgical means. Two main types of treatment are followed: injection of alcohol and nerve section.

Alcohol Injection

Alcohol has been injected into the peripheral branches of the nerve, namely, the supra- and infra-orbital nerves, by inserting a needle into their foramina; or into the mandibular division where it emerges from the foramen ovale, or where it enters the inferior dental foramen, or where it leaves the mental foramen. Ninety-five percent alcohol is injected to coagulate the nerve. In all these procedures the relief is temporary; pain and sensation return in six months to a few years. Deep alcohol injections of the foramen rotundum and ovale require a considerable amount of practice, for the nerves are at depths of 2 to 2½ inches. The procedure of alcohol ganglionic injection of Harris is quite dangerous and is generally not advisable. The alcohol might enter the subarachnoid space, the optic nerve, the oculomotor nerve or pons. The danger of damaging the sensory and sympathetic innervation of the cornea is great and a neurogenic keratitis may result. Also, the motor division may be interrupted more frequently than with retrogasserian neurotomy. It is always advisable as a first procedure to try alcohol injections, for they accustom the patient to the facial numbness. When section of the posterior root of the gasserian ganglion is carried out, numbness is permanent; but with the injection, numbness gradually disappears and the pain may return. The patient may again be offered the choice of numbness versus pain.

Section of Posterior Root

Section of the posterior root of the fifth nerve for trigeminal neuralgia is a satisfactory procedure. This is carried out by crushing or avulsing the nerve as well as actually cutting it. The mortality rate is less than 1% and the hospital morbidity is about seven to 10 days. The operation has been performed upon the very old, and even people with cardiac decomposition or atrial fibrillation may be treated surgically. The operation permanently destroys the sensory roots between the gasserian ganglion and the pons. The motor root is spared, as is the first division, except when it is necesary to relieve pain in that division. Occasionally the operation is followed by facial weakness; but this rarely lasts more than a few weeks. If the fibers to the ophthalmic division have been spared, one need have no concern for the eye. If it has been necessary to destroy all of the fibers and render the eye anesthetic, the patient's glasses should be fitted with a shield to keep foreign bodies out of the eye. The safest and most satisfactory method is by the temporal extradural approach, but this approach carries the added hazard of avulsion of the whole sensory root, thereby destroying tactile sensation in the cornea.

Some surgeons prefer the posterior approach through the cerebellopontine angle. They cut the root of the fifth nerve, but the risks to the patient are much greater. Compression of the ganglion has also been attempted and has effected relief in a number of cases. In 1937, Sjoqvist in Sweden developed a novel operation called intramedullary tractotomy, in which the

descending trigeminal tract was cut in the posterolateral aspect of the medulla oblongata, but the operation is potentially more hazardous and less certain than the standard retrogasserian neurotomy by the temporal approach. Though it has the advantage of destroying only pain sensibility in the face while leaving the sensation of touch intact, the procedure is now thought to be unreliable and is done only under very special circumstances.

Differential Diagnosis

A number of conditions must be differentiated from trigeminal neuralgia and should be thought of in all instances of facial pain in order that other serious and complicating diseases will not be overlooked. Included in the differential are the following. 1. Vasomotor facial neuralgia, which has a predilection for middleaged males, occurs with considerable regularity, usually appears during the night at the same time, and has associated with it injection of the conjunctiva, watering of the eye, possibly an ipsilateral Horner's sign and bradycardia during the attack. 2. Nasopharyngeal tumors, which account for 0.8% of all malignant tumors, have facial pain as their most frequently occurring neurological manifestation. 3. Other tumors, such as meningiomas, neurofibromas, epidermoid cysts, may also press upon the trigeminal nerve and/or the gasserian ganglion and give rise to facial pain. 4. Atypical facial neuralgia is a condition which affects high-strung or middle-aged women and is characterized by persistent or remitting pains in the head, face and neck which are not confined to the distribution of the fifth cranial nerve. 5. Dental pain may also simulate trigeminal neuralgia, although the pain is usually deeper in location and more continuous than that found in tic. 6. Sinusitis may likewise produce recurrent paroxysmal neuralgic facial pain, as may carcinoma of the sinuses. 7. Geniculate ganglion neuralgia is not a common disorder and is said to involve the deeper structures of the face and the auditory canal. 8. Temporomandibular neuralgia (Costen's syndrome) occurs in individuals who, by virtue of alterations in the bite, develop severe pain in the face in front of the ear, the character, duration, and distribution of the pain differentiating it from trigeminal neuralgia, with relief following correction of the malocclusion. 9. Herpes zoster of the trigeminal nerve does not differ except in distribution from the same affliction in a spinal nerve.

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References: 1. Gardner, H. L.: J. Miss. M.A. 8:529, 1967. 2. Porter, P. S., and Lyle, J. S.: Arch. Dermat. 93:402, 1966. 3. Walsh, H.; Hildebrandt, R. J., and Prystawsky, H.: Am. J. Obst. & Gynec. 93:904, 1965. 4. Vaginitis and the Pill: J.A.M.A. 196:731, 1966. 5. Guerriera, W. F.: South. M.J. 56:390, 1963. 6. Seelig, M. S.: Am. J. Med. 40:887, 1966. 7. To-day's Drugs, New York, Grune & Stratton, Inc., 1965, p. 316. 8. Gray, L. A., and Barnes, M. L.: Am. J. Obst. & Gynec. 92:125, 1965. 9. Salerno, L. J.; Ortiz, G., and Turkel, V.: Vaginitis: A Diagnostic and Therapeutic Approach, Scientific Exhibit, presented at the 115th Annual A.M.A. Convention, Chicago, Illinois, June 1966. 10. Walsh, J. C.; Sheffery, J. B., and Wilson, T. A.: Med. Ann. D.C. 37:358, 1968. 11. Nugent, F. B., and Myers, J. E.: Pennsylvania Med. 69:44, 1966.

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Case Report

Pulmonary Atresia

Ventricular Septal Defect, Atrial Septal Defect, Previous Right Blalock Anastomosis and Left Pott's Anastomosis—Complete Repair

JOSEPH C. KISER, M.D.
THEODORE A. PETERSON, M.D.
FRANK E. JOHNSON, M.D.
ROLF L. ANDREASSEN, M.D.
Minneapolis, Minnesota

ALTHOUGH CONSIDERABLE attention has recently been focused on the nebulous benefits of heart transplant, perhaps of greater importance is the progressive safety with which even complex forms of heart disease can be treated successfully by open techniques. We recently had the opportunity of caring for a young lady who required palliative shunt procedures for cyanotic heart disease during the period when open repair was not possible. She was fortunate to survive the formative years of open heart surgery until a time when complete repair could be carried out safely.

Case Report

A female, 26 years old. Cyanotic heart disease was noted at birth. A right Blalock procedure was performed at the age of three years* and a left Pott's anastomosis at age 13. She was improved with regard to degree of cyanosis and level of activity by both procedures. During the four to five years prior to this admission, she developed progressive dyspnea and peripheral

*1946—Johns Hopkins University, Dr. Alfred Blalock. Diagnostic evaluation by Dr. Helen Taussig.



Fig. 1—Posteroanterior chest x-ray. There is marked cardiomegaly, pulmonary congestion and evidence of a previous right and left thoracotomy.

edema. With the institution of digitalis, salt restriction and appropriate diuretics, subsequent to an episode of severe decompensation in 1968, she required no further hospitalization. However, she continued to have ease of fatigability and became dyspneic with mild exertion, such as making a bed or climbing one-half flight of stairs. She also complained of tightness and pain in the chest and noted occasional near syncope.

Physical Findings

On physical examination her blood pressure was 95/80 (right arm) and 125/80 (left arm). The femoral pulses were of good quality. She was markedly cyanotic (cyanosis involving the whole face but most prominent over the cheeks, tip of the nose, nailbeds and lower extremities). She became dyspneic when talking. The neck veins were markedly distended. The heart appeared enlarged with a prominent right ventricular lift. There was a continuous murmur heard over the entire left upper chest, both in front and in back. A similar murmur was audible but less prominent to the right of the sternum. There was a harsh grade V systolic murmur heard over most of the precordium, but loudest at the apex, where there was a prominent systolic thrill. The second sound was soft. The liver was palpable four centimeters below the right costal margin. There was pedal edema and the skin had the brawny appearance of chronic stasis. The hemoglobin was 20.2 and the hematocrit was 62.5. The chest x-ray is shown in Figure 1. The electrocardiogram indicated right ventricular hypertrophy with incomplete right bundle branch block and evidence of right atrial hypertrophy.

Cardiac Catheterization

Cardiac catheterization was performed with considerable difficulty due to extremely large chambers and obvious tricuspid incompetence. The pressure in both ventricles was at systemic level with elevation of the end diastolic pressure (130 over 20 to 26 millimeters of mercury). The pulmonary artery could not be entered.

Angiography

Following injection into the left ventricle, dye entered the aorta, traversed a large ventricular septal defect to enter the right ventricle, and then regurgitated into the right atrium. No dye entered the pulmonary artery. The right and left pulmonary arteries were demonstrated to be normal in size. The presence of a ventricular septum was confirmed. The exact orientation of the great vessels was not clear because of considerable dilution of the contrast media, although the aorta appeared to arise from the left ventricle. There did appear to be a narrow infundibulum arising from the right ventricle. It was not possible to accurately assess the pulmonary resistance. Injection of the innominate artery demonstrated the Blalock anastomosis

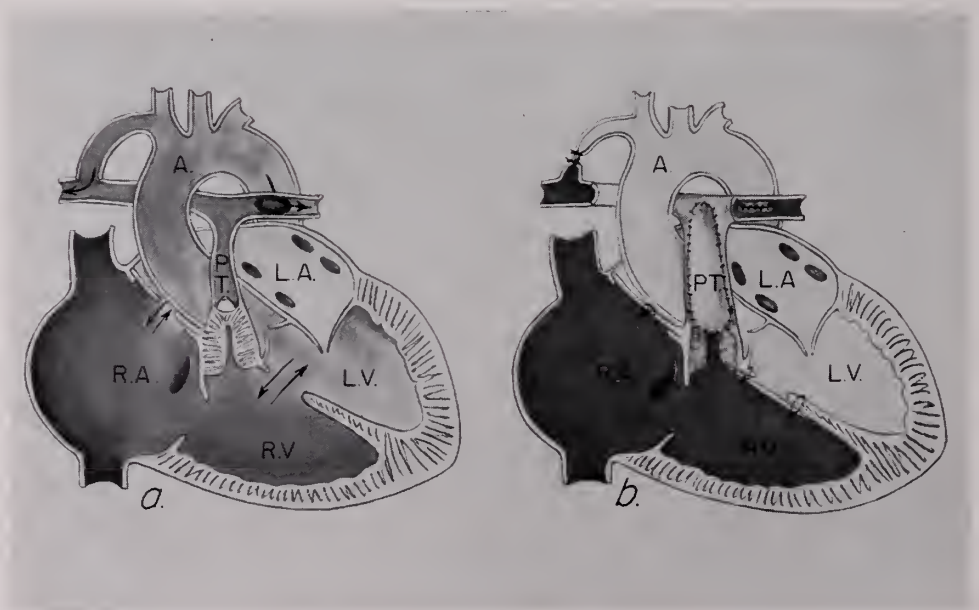


Fig. 2—Diagrammatic representation of the operative findings (a) and surgical repair (b). The dark shading indicates unsaturated venous blood. There was bi-directional shunting at atrial and ventricular levels. Unsaturated blood reached the lungs via the right subclavian artery to right pulmonary artery anastomosis (Blalock) and via the left-sided aorta to left pulmonary artery anastomosis (Pott's). Marked functional tricuspid incompetence was present.

to be patent, and injection of the distal aorta proved the left Pott's anastomosis to be functioning.

Surgery

Open heart surgery was performed on March 3, 1969. The operative findings and the repair are summarized in Figure 2. The chest was entered through a medial sternotomy. There was severe dextroposition of the aorta. The main pulmonary artery was extremely small, measuring 7 to 8 millimeters in diameter. It was nearly directly posterior, but slightly to the left of the aorta, which measured 5 centimeters in diameter. The heart was markedly enlarged in all chambers. There was no evidence of a left superior vena cava. There was a palpable thrill over the surface of the right atrium and the left pulmonary artery. Intracardiac exploration revealed marked tricuspid incompetence and an atrial septal defect measuring 2 centimeters in diameter. Pressures were measured (right atrium, 16 to 18 mm/Hg; left atrium, 22 to 24 mm/Hg; right and left ventricle, 80/12 mm/Hg; pulmonary artery, 20 mm/Hg; aorta, 80/60 mm/Hg).

Operative Procedure

The right Blalock anastomosis was dissected within the pericardium and a heavy silk ligature was passed around it. Temporary extracorporeal circulation was instituted and the right Blalock was ligated. Manually compressing the left Pott's, the body temperature was reduced to 23 degrees centigrade. Total circulatory arrest for a period of 16 minutes was required to close the left Pott's through an incision in the left pulmonary artery. Air was carefully evacuated from the aortic arch and total bypass was re-instituted and maintained at 30 degrees centigrade for the remainder of the procedure. A large ventricular septal defect was closed with a teflon patch. Resection of the severe infundibular pulmonary stenosis was accomplished through the right ventriculotomy. A long on-lay pericardial patch was used to correct the pulmonary atresia. The atrial septal defect was repaired by direct suture. Total by-pass time was three hours and 12 minutes. Re-operation in the early postoperative period was necessary to control bleeding. Digitalis and assisted ventilation were required for support during a protracted convalescence. The patient was discharged from the hospital on the 24th operative day.

She is now 12 months postoperative and her level of activity is markedly improved. She has a moderate systolic murmur audible along the lower left sternal border and a soft systolic murmur with a short diastolic component in the pulmonic area. She has had no tendency toward fluid retention and denies dyspnea. Her heart remains enlarged. The hemoglobin is now 13.5 and the hematocrit 43.5.

Discussion

Congenital pulmonary atresia is an uncommon lesion and is considered a severe manifestation of tetralogy of Fallot. Although the pulmonary valve, pulmonary ring and main pulmonary artery may be severely hypoplastic, the left and right pulmonary arteries are often near normal size, allowing correction of the entire malformation. In the absence of a patent ductus or some surgical contribution to pulmonary flow, such as the Blalock and the Pott's anastomosis in this case, the development of extensive bronchial collateral vessels is necessary for survival.

Cardiac catheterization was performed to assess the anatomy and to measure the pulmonary vascular resistance, recognizing that the presence of a common ventricle, excessive pulmonary vascular resistance (sometimes seen subsequent to a Pott's anastomosis), or deformity of the left or right pulmonary arteries would preclude a successful repair. Because of the massive enlargement of all cardiac chambers and the presence of severe functional tricuspid valve incompetence, catheterization was technically difficult. With the pulmonary atresia, neither catheter nor dye could enter the pulmonary artery to define the anatomy of the main pulmonary artery prior to surgery. This prevented a direct assessment of the pulmonary resistance. However, under optimal circumstances, accurate assessment of pulmonary vascular

resistance in the presence of two functioning systemic to pulmonary shunts is uncertain. The clinical finding of a continuous murmur, in the absence of extensive bronchial collateral vessels and the large flow across the Pott's anastomosis on angiography, provided the best evidence for the absence of high pulmonary resistance. The intraoperative finding of a low pulmonary artery pressure confirmed this clinical impression. It may be that reconstruction of the main pulmonary artery with a homograft, recently described by Drs. Wallace and McGoon,[1] may be superior to the patch technique since the latter allows pulmonary valvular incompetence. It was felt, however, that the pulmonary regurgitation would be reasonably well tolerated since the pulmonary vascular resistance appeared to be low in this case.

Successful closure of a previous Pott's anastomosis presents technical difficulties, but it is possible with a high degree of safety using the technique described by Kirklin et al. in 1961.[2] The ventricular and atrial septal defects were of the usual variety. With the improvement in hemodynamics, effected by the closure of the large left to right shunts and by providing an exit from the right ventricle into the pulmonary artery, it is anticipated that the tricuspid incompetence will become progressively less severe.

Current techniques of open heart surgery allow repair of complex cardiac malformations with a high degree of safety. This is a report of a moderately complex congenital cardiac malformation, further complicated by two previous systemic to pulmonary artery shunts, successfully repaired using well developed methods.

The authors are indebted to Dr. Cecil J. Watson and the Teaching Service at the Northwestern Hospital, Minneapolis, Minnesota, for their excellent assistance in the care of this desperately ill patient.

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*Dr. George Crane: The Quotable Dr. Crane, 1968.

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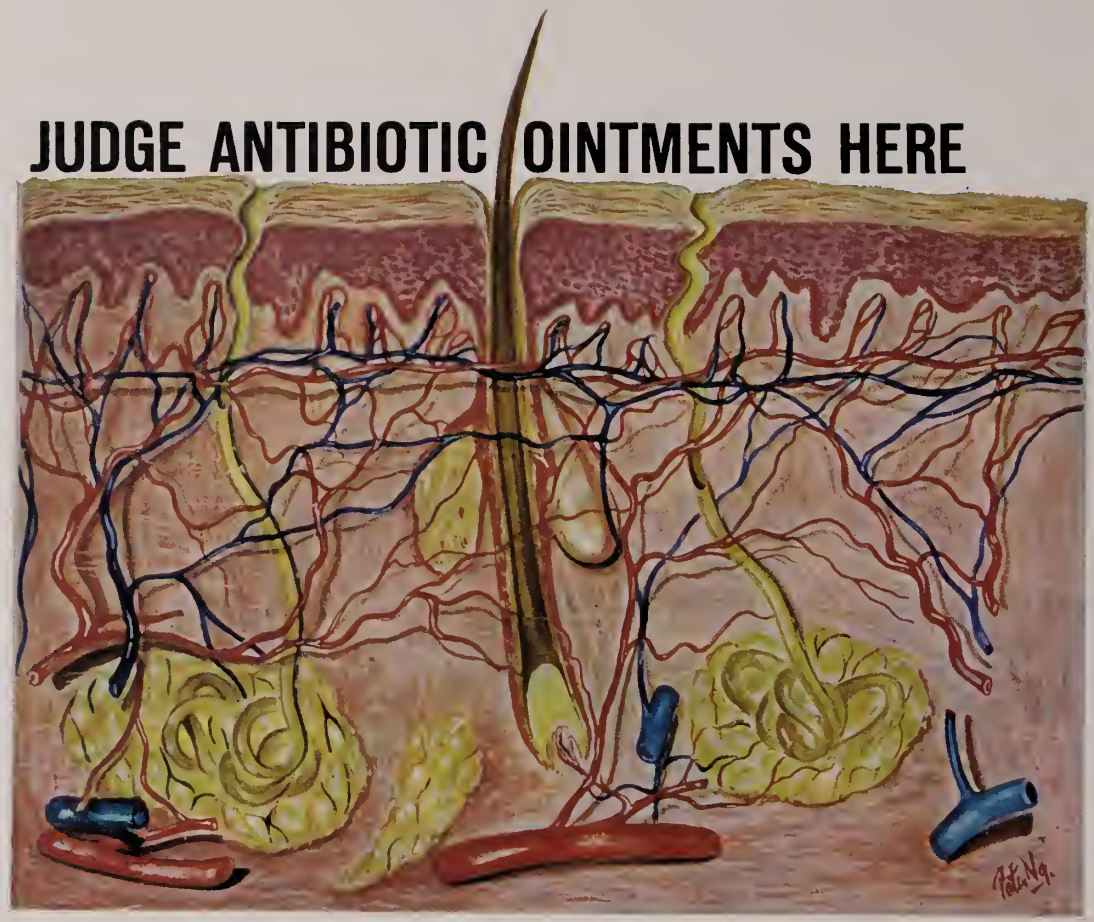
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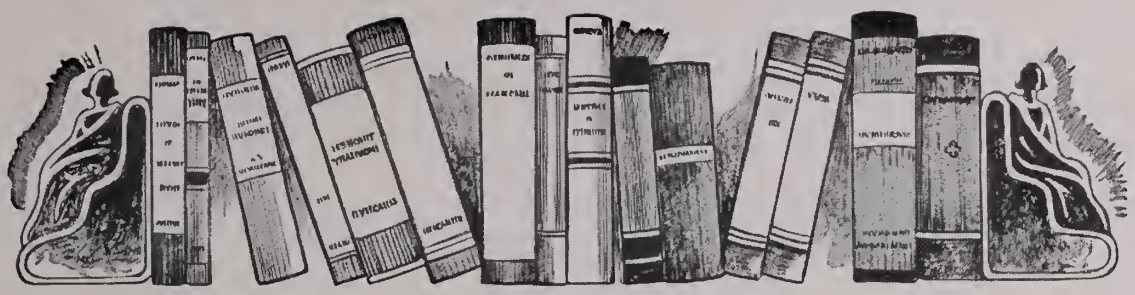
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Book Reviews

CARDIAC ARREST AND RESUSCITATION. By Hugh E. Stephenson, Jr. Third edition 1969. C. V. Mosby. St. Louis. 660 pp., $29.50.

Hugh E. Stephenson is professor of surgery at the University of Missouri in Columbia and has been writing on the subject of cardiac arrest and resuscitation throughout his professional life, this being the third edition of a book that first appeared in 1957. Every physician dealing with live people knows that he may suddenly become the attending physician at the bedside (or streetside) of a patient suffering cardiac arrest; it therefore behooves all of us to make some preparation for a course of action to be pursued in such an event. To those who demur, saying that their specialty is too far removed, their skill too attenuated to permit them to attend a patient in such a crisis, one can only refer them to Stephenson's comprehensive chapter on medicolegal aspects of cardiac arrest and resuscitation. One speculates whether a preconceived plan of action might have changed the procedure of one surgeon who, faced with cardiac arrest after tonsillectomy in a 32-year-old woman, first ran to the husband in the waiting room to obtain consent for emergency thoracotomy.

Numerous contributors have supplied chapters. Negovskii writes of reanimatology in the Soviet Union and advises arterial transfusion when blood loss complicates cardiac arrest. One wonders how blood in the Soviet Union can be made so quickly available. In this country the whole acute course of cardiac arrest from onset to recovery is long completed before the laboratory technician sits down to type the blood.

This reviewer considers Stephenson too ready to resort to open massage in cardiac arrest. However, he is most persuasive about opening the chest in the first trial if closed massage and assisted respiration are unsuccessful.

Reuben Berman, M.D.
Minneapolis, Minn.

MODERN TREATMENT — TREATMENT OF CONGENITAL HEMORRHAGIC DISORDERS. Edited by Oscar D. Ratnoff, M.D.
TREATMENT OF DISORDERS OF GROWTH AND DEVELOPMENT. Edited by Oscar D. Ratnoff, M.D. Volume 5, No. 1. Harper & Row, Hoeber Medical Division.

The first symposium on congenital hemorrhagic disorders is limited to hereditary disorders of blood clotting. These articles will be valuable for quick reference because each of the articles is complete and can be read independently of the series.

The second symposium on disorders of growth and development is organized along the approach of the endocrinologist. Nevertheless, the section will be valuable to any physician who is up against this most perplexing of pediatric problems. This section is recommended as an antidote to the frustration which a clinician so often feels as he approaches a child who has delayed or abnormal growth.

Warren J. Warwick, M.D.
Minneapolis, Minnesota

PRACTICAL UROLOGY. Author: Chester C. Winter, M.D., Publisher: C. V. Mosby Co., St. Louis, Missouri, Price: $11.00, Pages: 247.

This is a well written monograph. It is concise and covers the field of urology sufficiently to make it a good reference book for the student or for use in the doctor's office.

The questions and selected reading at the end of each chapter are an intriguing innovation for the individual who enjoys checking his knowledge.

Carl O. Rice, M.D.
Minneapolis, Minnesota

THE ROLE OF LEARNING IN PSYCHOTHERAPY—A CIBA Foundation Symposium. Edited by Ruth Porter, Little, Brown and Company, 1968.

This book is about a three-day symposium put on by the CIBA Foundation, involving men from different schools of psychotherapy, whose task was to discuss the role of learning in psychotherapy. The book is divided into ethology, validation of results in psychotherapy, learning with emphasis on techniques in education and treatment, and prospects for the future.

It was the feeling of the members of this symposium that the psychoanalyst's main goal is to give insight to the patient; while that of the behavior therapist is to derive insight into the problem himself, rather than developing it in the patient. One of the arguments was that in psychoanalytic-oriented therapy as contrasted with behavior therapy, the underlying cause of the problem is not treated. This aspect was discussed in the context that treating symptoms alone may well result in the patient acquiring new and possibly more maladaptive symptoms. The behaviorists noted that while a patient may learn insight under the psychoanalytically-oriented therapy, he still may not use this knowledge to change his maladaptive behavior. They felt that the most important facet of therapy is good history-taking, followed by the employment of the information derived from the history as a "basis" for sound judgment in guiding the therapy, thus enabling the therapist to discriminate between the patient's reported problems and his "real" problems. Under this approach, the history-taking would be done differently, with more emphasis on an active approach than would be the case with the history taken by a psychoanalyst.

The entire symposium was excellent, very informative, and interestingly presented. This book is worth reading for those interested in learning more about the different psychotherapies, the evaluation of their end results, and the extent to which learning plays a role in the outcome.

Thomas Dredge, Jr., M.D.
Minneapolis, Minnesota

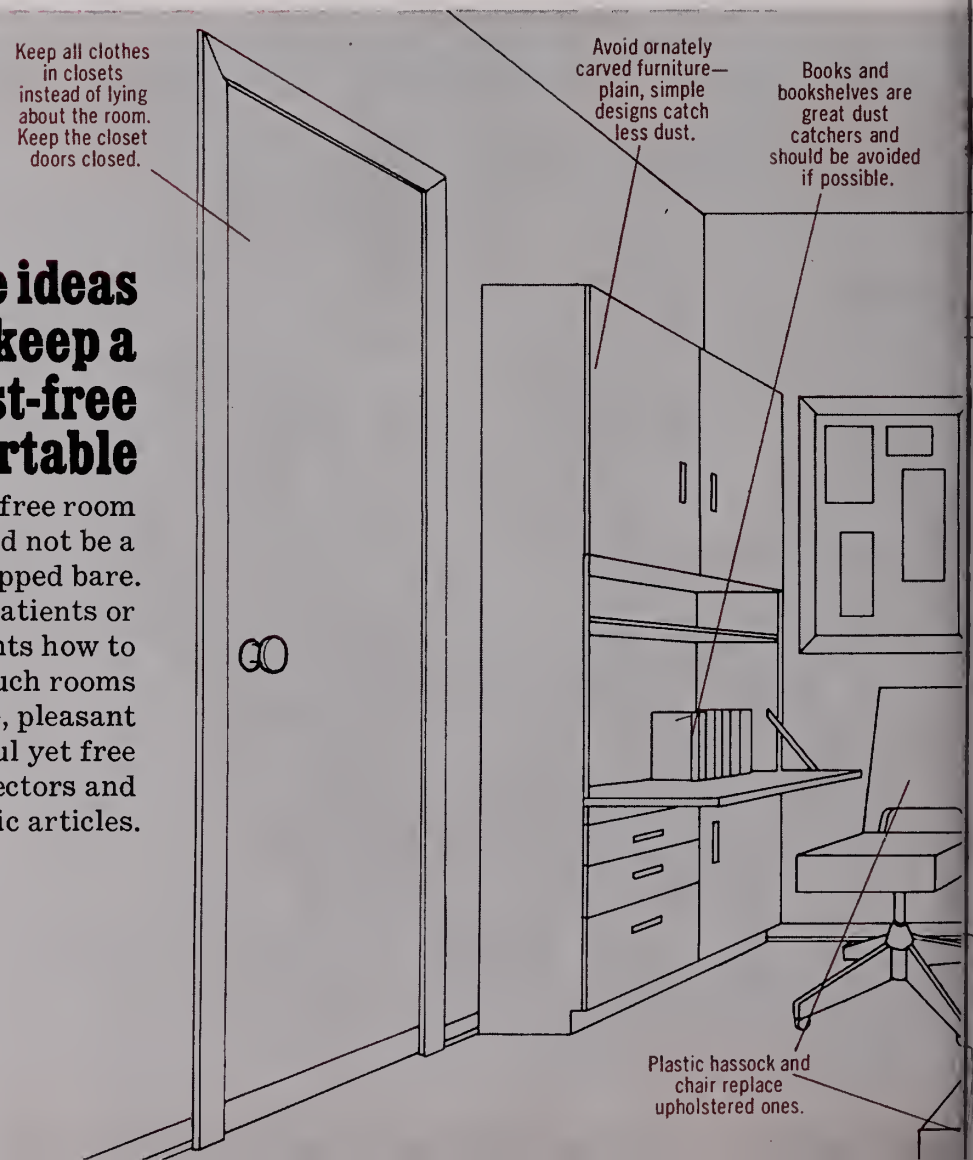
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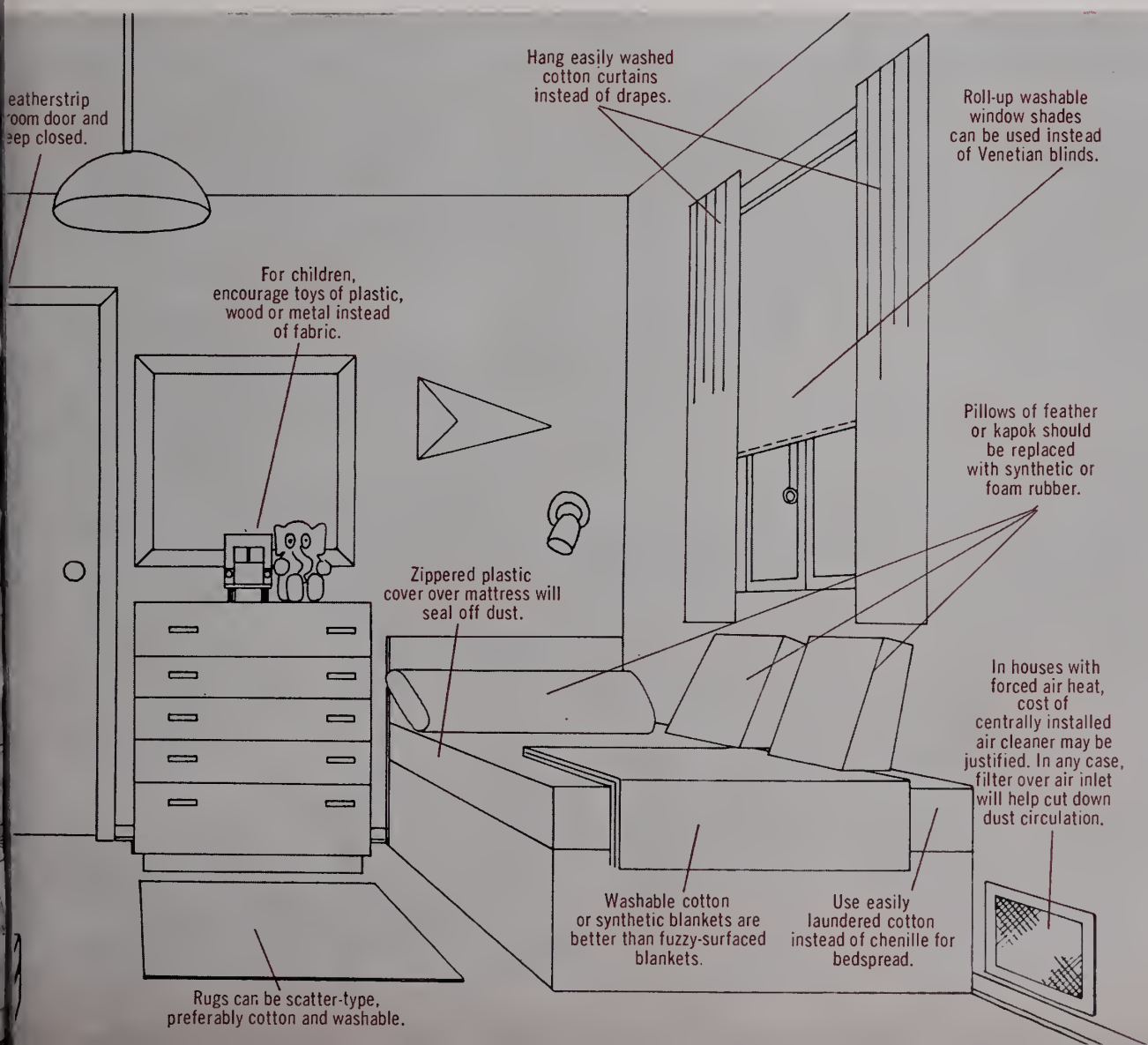
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Clinical Path Conference

Mitral Valvular Involvement Secondary to Bacterial Endocarditis of Aortic Valve

Dr. Kyung Soon Lee:

A 67-year-old man was admitted for cardiac evaluation. The patient stated that, after having rheumatic fever at the age of 16 years, he made a good recovery and had worked all his life as a grader in construction work. Five years ago, shortness of breath became apparent and congestive cardiac failure with mitral valvular disease was diagnosed. He improved satisfactorily with medical treatment. Four years ago, after an injury to the thorax while at work, he was frequently thirsty and passed large volumes of urine. Diabetes mellitus was diagnosed and he was treated with diet and oral hypoglycemic drugs. Eighteen months ago weakness appeared and anemia was observed. The diagnosis of subacute bacterial endocarditis was made, for which penicillin was administered for 21 days. Recovery followed and the patient remained well until two months ago when extreme shortness of breath and swelling of the legs developed.

Physical examination showed a well developed man with labored breathing. The blood pressure was 120/100 mm. Hg; the oral temperature, 98.6° F.; the pulse rate, 120 per minute. The conjunctiva were normal. The cervical veins were moderately distended. The thorax was symmetrical. Rales were heard at the left pulmonary base. The cardiac rhythm was irregularly irregular. The first cardiac sound was not accentuated. There was a grade IV/VI pansystolic murmur at the apex which was well transmitted to the left axilla. The intensity of the murmur diminished with inspiration. The second cardiac sound was accentuated. A high frequency diastolic murmur was present at the aortic area. At the apex a third heart sound was followed by a short diastolic rumble. The hepatic edge extended just below the costal margin. There was mild pitting edema of the legs.

The results of laboratory studies of urine, blood counts, blood erythrocyte sedimentation rate, blood urea nitrogen, electrolytes and cholesterol were within normal limits. The fasting blood sugar was 116 mg. per 100 ml. of blood (normal, up to 95 mg.) and the value for uric acid was 10.3 mg. per 100 ml. serum (normal, up to 6.5 mg.). The electrocardiogram showed

atrial fibrillation with rapid ventricular response and left ventricular hypertrophy (Figure 1).

Dr. Johnson, would you describe the roentgenographic observations?

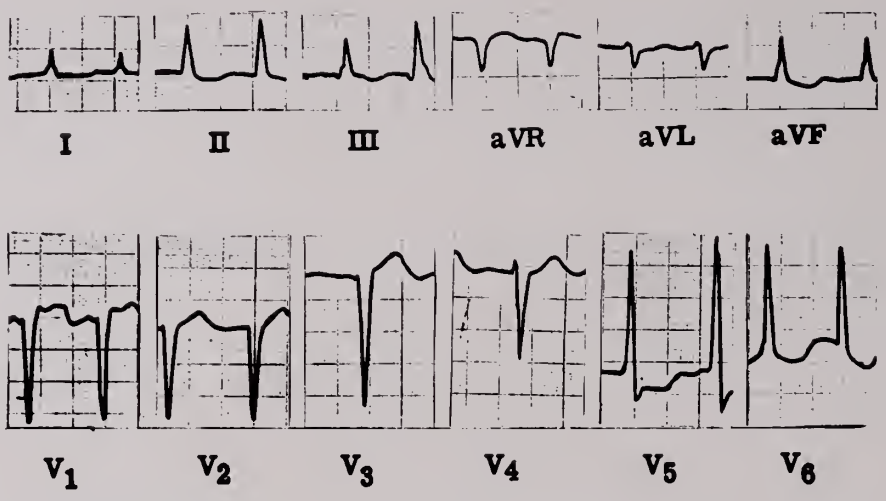


Fig. 1—Electrocardiogram. Selected ventricular complexes are shown from the electrocardiogram in which atrial fibrillation was present.

Dr. Thomas Johnson:

Thoracic roentgenograms (Figure 2) revealed moderately severe left ventricular hypertrophy and central pulmonary vascular congestion. A small left pleural effusion was present.

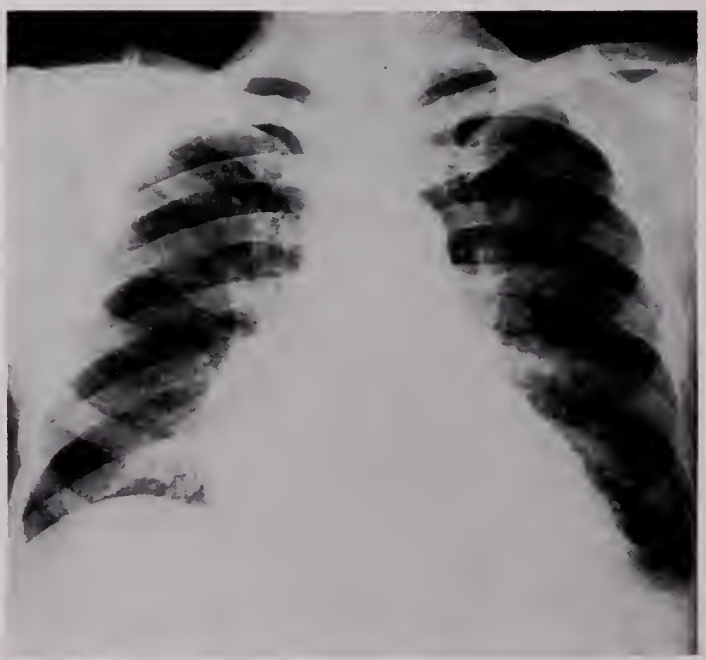


Fig. 2—Thoracic roentgenogram in frontal view. Moderate cardiomegaly suggesting left ventricular hypertrophy and central pulmonary venous congestion. Evidence of a small, left pleural effusion also appears.

Dr. Lee:

Thank you. The results of cardiac catheterization are shown in the Table. These reveal pulmonary hypertension associated with abnormally high pulmonary arterial wedge pressures associated with huge cardiovascular waves (Figure 3). There was no sign of a shunt. The low cardiac output was associated with a marked difference in saturation of arterial and mixed venous blood. Distortion of the indicator dilution curves was characterized by a prolonged appearance time, a low peak concentration and a slurred disappearance slope.

Dr. Karnegis, would you please discuss the differential diagnosis?

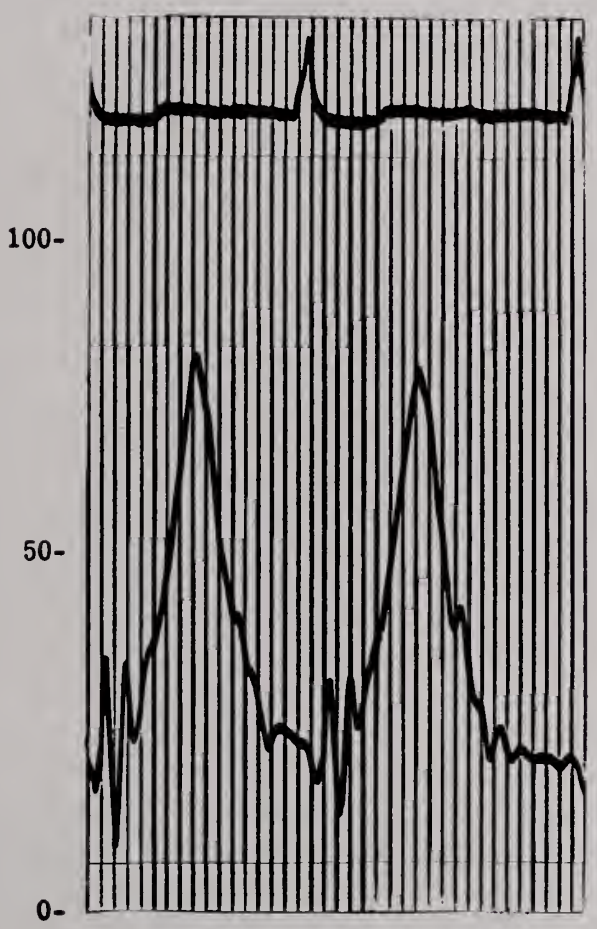


Fig. 3—Pulmonary "arterial wedge" pressures showing huge CV waves. Electrocardiogram appears above. Numbers along ordinate indicate pressure in millimeters of mercury.

Dr. James N. Karnegis:

Five years ago the patient developed congestive cardiac failure and a murmur was heard. The cardiac history may extend even further back, since there was a possible history of rheumatic fever as a youth. The injury to the chest and the diabetes mellitus are probably incidental to the cardiac condition.

Subacute bacterial endocarditis was diagnosed and apparently successfully treated eighteen months ago. The patient did well for over a year, but then severe cardiac failure ensued.

TABLE
Results of Cardiac Catheterization

Site	Pressure (mm.Hg)	Oxygen Saturation (per cent)
Right atrium	c21 v22 (mean 20)	49
Pulmonary arterial wedge	cv80 (mean 42) end-diastolic 26	—
Right ventricle	82/3, 20	—
Pulmonary artery	90/46 (mean 70)	46
Brachial artery	160/98 (mean 113)	100
Left ventricle	180/2, 28	—
Left ventricle	152/2, 32	—
Aorta	152/102	—

Cardiac index 1.7 L./min./M².

The indicator dilution curves showed a prolonged appearance time, low peak concentration, and a slurred disappearance slope.

Physical examination at the time of referral suggested cardiac failure and multiple valvular disease. The results of the examination suggest that aortic and mitral insufficiency were present and possibly also some mitral stenosis.

The findings of cardiac catheterization confirm the presence of severe mitral insufficiency. There was no evidence for aortic stenosis or mitral stenosis. The patient had severe pulmonary hypertension and severe biventricular decompensation. The heart was unable to supply an adequate amount of blood to the body, as evidenced by the low cardiac index. This also accounts for the very low pulmonary arterial blood oxygen saturation level and the extreme arteriovenous blood oxygen saturation difference. The indicator dilution curves were distorted, as is seen in low cardiac output and valvular insufficiency states. Could we please see the results of angiocardiography?

Dr. Johnson:

Left ventriculography performed by passing a catheter into the left ven-



Fig. 4—Left ventriculogram in frontal (*a*) and lateral (*b*) views. Signs of mitral insufficiency. Opacification of enlarged left atrium indicating mitral insufficiency.

tricle in retrograde fashion from the aorta showed gross mitral insufficiency with engorgement of the left atrial appendage and the proximal segments of the pulmonary veins. The left atrial chamber was enlarged (Figure 4). Mild aortic insufficiency was demonstrated by aortography.

Dr. Karnegis:

We are faced with a hemodynamic situation of severe mitral insufficiency and mild aortic insufficiency.

The question that remains is the etiology of these conditions. The patient gave a history of rheumatic fever. A useful clinical guide is that the adult patient with multiple valvular lesions usually suffers from rheumatic cardiac disease, especially if the valvular problems include aortic and/or mitral stenosis. The case under consideration demonstrated only valvular insufficiencies. The pulmonary arterial wedge pressure tracing is of interest, since it showed very high and sharp "cv" waves. This indicates mitral insufficiency, but the contour is similar to that recorded when the mitral insufficiency is of acute onset, such as from rupture of chordae tendineae or of a papillary muscle. The history here is long, however, comprising at least five years and perhaps more. Cardiac valves which are abnormal from any cause are known to be susceptible to infection and bacterial endocarditis. There was no evidence of active endocarditis at the time of the present admission.

I believe I must assume that this patient had rheumatic cardiac disease. Other forms of cardiac disease, such as congenital valvular lesions, both statistically and within the confines of this case history, are much less likely and I doubt their diagnosis can be warranted from the available information. Surgical intervention appears indicated.

Dr. Lee:

An operation was performed and we shall ask Dr. Hunter to describe the operative findings.

Dr. Samuel Hunter:

When the heart was exposed, both atria were found to be considerably enlarged. Under conditions of cardiopulmonary hypothermia (28-29° C.) and induced ventricular fibrillation, the left atrium was opened and the region of the mitral valve exposed.

The orifice of the valve was enlarged and considerable valvular tissue appeared to have been destroyed. One of the chordae attached to the anterior leaflet was identified as ruptured. The mitral valve was removed and replaced by the largest Beall valve. At the conclusion of the operation, the patient's condition was stable with systemic systolic blood pressures being 120 mm. Hg, systolic and 80, diastolic.

The patient recovered from anesthesia soon after completion of the operation.

During the first evening following the operation, the circulation suddenly deteriorated (systolic blood pressure, 70). In spite of some improvement with transfusions, later the same evening respiration became labored and breathing stopped. Attempts at resuscitation were unsuccessful.

Dr. Lee:

Thank you, Dr. Hunter. Dr. Edwards, would you please describe the pathologic findings?

Dr. Jesse E. Edwards:

We have to report on two phases, the specimen of mitral valve removed at operation and the necropsy.

The mitral valvular tissue was represented by several fragments of valve, one of which was identifiable as the anterior mitral leaflet. This showed irregular thickening at the area of closure. Attached chordae were matted together and a calcified vegetation was attached to the end of one of the chordae tendineae.

Histologically (Figure 5) the removed valvular tissue showed features of healed bacterial endocarditis with evidence of destruction of valvular tissue and reactive fibrosis. Vegetations attached to valvular surfaces contained calcified masses. A few leukocytes were present in the tissues surrounding calcified foci.

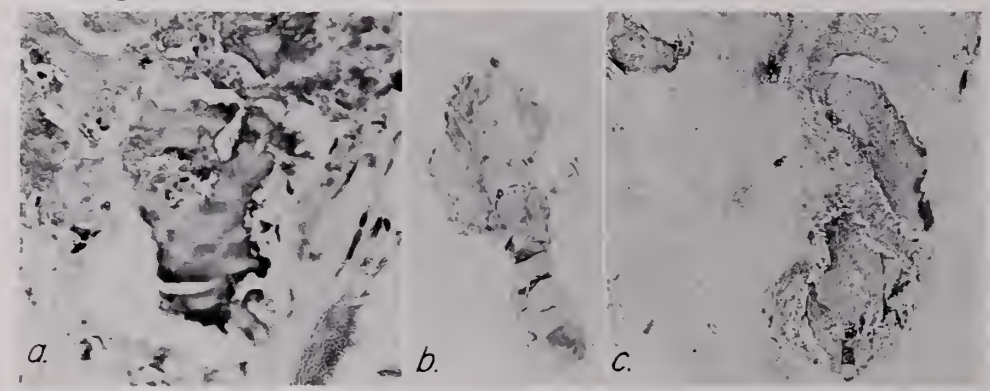


Fig. 5—Photomicrographs of portions of mitral valve excised surgically. (*a*) A portion of valvular tissue showing encapsulated calcified vegetative material. H & E; × 210. *(b)* Bulbous end of a ruptured mitral chord shows vegetative material. H & E; × 5.5. *(c)* Higher-power view of vegetative material attached to ruptured end of chord shown in *(b)*. The vegetation is composed of fibrin, platelets, and calcific masses. Some fibrous tissue is also present. H & E; × 20.

At the extremity of a ruptured chord, similar vegetations were attached.

In the necropsy, the findings of major significance were seen in the thorax. There was major cardiac enlargement, the heart weighing 800 grams. The chief basis for the cardiomegaly was major hypertrophy of the left ventricle. Moderate enlargement of the right ventricle was also a feature.

Of particular interest was the appearance of the aortic valve. This showed the features of a congenital bicuspid valve in which the cusps were oriented in anterior and posterior positions, the anterior cusp being the larger of the two.

As is characteristic of congenital biscuspid aortic valves, a shallow raphe extended from the aortic wall onto the aortic aspect of the center of the larger cusp. At the center of the free edge of the anterior cusp, a deformity represented by a convexity along the free margin was identified. At the edges of the convexity, the tissue was thickened. Opposite the abnormality of the anterior cusp, the posterior cusp showed a focus of fibrous thickening which coincided with the lesion of the anterior cusp. Histologic examination of the aortic valve revealed signs compatible with healed bacterial endocarditis. A section made through the deformed anterior cusp showed major fibrous thickening of the distal half of the cusp, the thickening being the result of deposit of laminations or dense collagen. In the cusp, at the junction of the distal and proximal halves of the cusp, there was a focus of calcification surrounded by dense fibrous tissue. The valves in the right side of the heart

were not remarkable. The lungs were edematous and pleural effusion of 300 cc. of fluid was present in the left pleural cavity.

The pathogenesis of the conditions observed in this case appear to be as follows. The primary condition is a congenital bicuspid aortic valve. The lesions seen on the valve are consistent with healed bacterial endocarditis.

The mitral valve also showed evidence of bacterial endocarditis with destruction of the leaflet tissue and rupture of at least one chord.

The association of aortic and mitral bacterial endocarditis is of interest. In most instances, the infection starts in one valve and moves to the other. It may start at the mitral valve and involve the aortic valve secondarily; or the infection may start on the aortic valve and, through regurgitation at the aortic valve, secondary "regurgitant infection" of the mitral valve may occur. The evidence in this case supports the concept that the primary site of infection was on the aortic valve, although clinically the secondary effect upon the mitral valve, with forms of mitral insufficiency, was the dominant lesion, and that the mitral valvular infection was secondary to the effects of

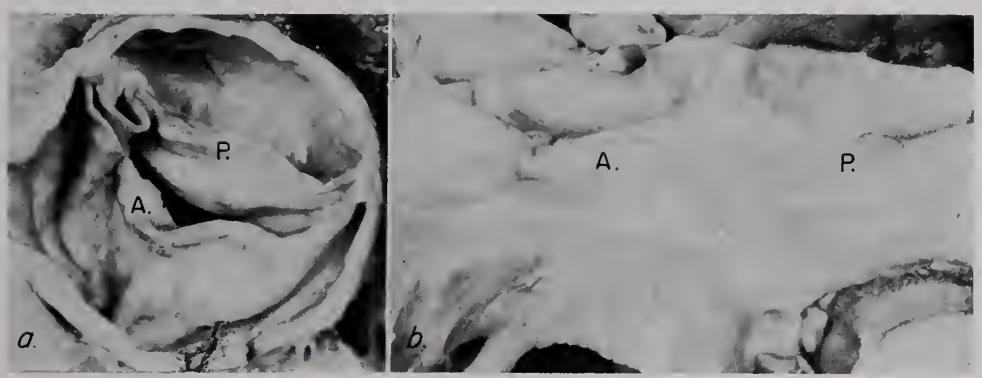


Fig. 6—The aortic valve. (*a*) Unopened valve viewed from above. The valve is bicuspid. The larger cusp lies anteriorly "A," the smaller posteriorly "P." The free edge of the anterior cusp is deformed by a concavity surrounded by thickening of the tissue. The posterior cusp shows focal thickening at a zone corresponding to the lesion in the anterior cusp. (*b*) The aortic valve opened. The deformity characterized by concavity of the anterior cusp "A" is easily evident. The fibrous thickening of the posterior cusp "P" is also apparent.

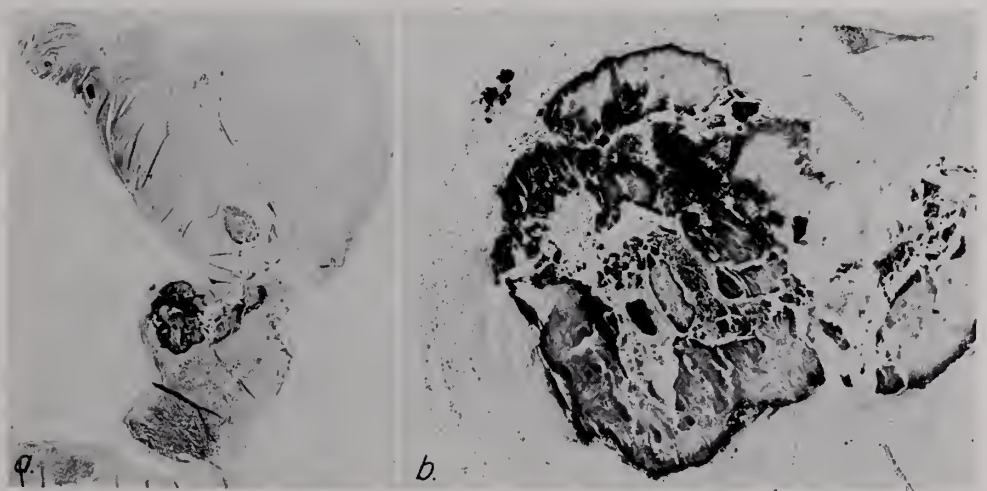


Fig. 7—Photomicrographs of aortic valve. *(a)* Low-power view of distal end of anterior cusp at zone of deformity seen in Figure 6. The distal end of the cusp shows bulbous thickening by laminated collagenous tissue. Proximal to this zone, there is an area of encapsulated calcific material. The latter is shown in higher power in *(b)*. H & E; × 22. *(b)* Focus of calcific material seen in the aortic cusp illustrated in *(a)*. Calcific material is surrounded by a fibrous capsule. H & E; × 54.

aortic bacterial endocarditis.

Although aortic insufficiency was identified clinically, it is evident that the major functional disturbance was mitral insufficiency. This phenomenon, namely, major mitral insufficiency secondary to mild aortic insufficiency of infectious origin, is not unique and we have observed this combination in a number of cases studied previously.[1]

This case represents an entity in which mitral insufficiency evolves as a dominant hemodynamic disturbance in some instances of aortic valvular bacterial endocarditis.

The case also serves to emphasize the point that serious hemodynamic sequelae of bacterial endocarditis may remain even though the infectious aspect of the disease has been overcome.

Yet another classical feature of this case is the presence of a congenital bicuspid aortic valve as a condition favoring the development of bacterial endocarditis.

Diagnosis

Mitral valvular involvement secondary to bacterial endocarditis of aortic valve.

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James N. Karnegis, M.D.*
Samuel Hunter, M.D.*
Jesse E. Edwards, M.D.*
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*From the Department of Pathology, Radiology, Medicine and Surgery, The Charles T. Miller Hospital, St. Paul, Minnesota and The University of Minnesota, Minneapolis, Minnesota.

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Substance, Not Shadow

Shakespeare characterized old age as:

Second childishness and mere oblivion,
Sans teeth, sans eyes, sans taste, sans everything.

If this were the only prospect looming on the far horizon of human life, men and women would fervently pray that they might quit this world of tribulation before the evil days came. But the ideal of old age which they cherish is something very different. They wish a green old age, but a green old age with the power to enjoy still undiminished. Longevity connotes for such not benumbing senility, but full-blooded existence, a life which till the last dread hour shall be lived in tolerable possession of physical and mental faculties. In fine, they crave the substance, not the shadow.*

*W. Forbes Gray: Five Score, 1931.



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Actions—Ovulen acts to prevent ovulation by inhibiting the output of gonadotropins from the pituitary gland. Ovulen depresses the output of both the follicle-stimulating hormone (FSH) and the luteinizing hormone (LH).

Special note: Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. Both types provide almost completely effective contraception.

An increased risk of thromboembolic disease associated with the use of hormonal contraceptives has now been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure, liver disease and reduced tolerance to carbohydrates, have not been quantitated with precision.

Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency of some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can be neither affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

Indication—Ovulen is indicated for oral contraception.

Contraindications—Patients with thrombophlebitis, thromboembolic disorders, cerebral apoplexy or a past history of these conditions, markedly impaired liver function, known or suspected carcinoma of the breast, known or suspected estrogen-dependent neoplasia and undiagnosed abnormal genital bleeding.

Warnings—The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism and retinal thrombosis). Should any of these occur or be suspected the drug should be discontinued immediately.

Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis and pulmonary embolism and the use of oral contraceptives. There have been three principal studies in Britain[1-3] leading to this conclusion, and one[4] in this country. The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about sevenfold, while Sartwell and associates[4] in the United States found a relative risk of 4.4, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as nonusers. The American study also indicated that the risk did not persist after discontinuation of administration, and that it was not enhanced by long-continued administration. The American study was not designed to evaluate a difference between products. However, the study suggested that there might be an increased risk of thromboembolic disease in users of sequential products. This risk cannot be quantitated, and further studies to confirm this finding are desirable. Retrospective studies in Great Britain and the United States have shown a statistically significant association between cerebral thrombosis and embolism and the use of oral contraceptives.

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions medication should be withdrawn.

Since the safety of Ovulen in pregnancy has not been demonstrated, it is recommended that for any patient who has missed two consecutive periods pregnancy should be ruled out before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule the possibility of pregnancy should be considered at the time of the first missed period.

A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time.

Precautions—The pretreatment and periodic physical examinations should include special reference to the breasts and pelvic organs, including a Papanicolaou smear since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals. Endocrine and possibly liver function tests may be affected by treatment with Ovulen. Therefore, if such tests are abnormal in a patient taking Ovulen, it is recommended that they be repeated after the drug has been withdrawn for two months. Under the influence of progestogen-estrogen preparations preexisting uterine fibromyomas may increase in size. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam adequate diagnostic measures are indicated. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. Any possible influence of prolonged Ovulen therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives.

The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving Ovulen therapy. The age of the patient constitutes no absolute limiting factor, although treatment with Ovulen may mask the onset of the climacteric. The pathologist should be advised of Ovulen therapy when relevant specimens are submitted. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids.

Adverse reactions observed in patients receiving oral contraceptives—A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions: thrombophlebitis, pulmonary embolism and cerebral thrombosis.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, breast changes (tenderness, enlargement and secretion), change in weight (increase or decrease), changes in cervical erosion and cervical secretions, suppression of lactation when given immediately post partum, cholestatic jaundice, migraine, rash (allergic), rise in blood pressure in susceptible individuals and mental depression.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: anovulation post treatment, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption and itching.

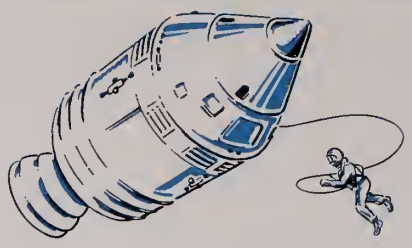
The following laboratory results may be altered by the use of oral contraceptives: hepatic function: increased sulfobromophthalein retention and other tests; coagulation tests: increase in prothrombin, Factors VII, VIII, IX and X; thyroid function: increase in PBI and butanol extractable protein bound iodine, and decrease in T^3 uptake values; metyrapone test and pregnanediol determination.

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Dermatology

Dermatitis of the Hands

Dermatitis of the hands is a common disorder. Many of the patients are housewives whose hands come in contact with many cutaneous irritants. Eczema is a term which is difficult to define; its meaning depends largely on the particular concept of the individual physician. It is a common, superficial, inflammatory dermatosis which does not belong to any other recognized dermatologic category. The acute phase is characterized by vesiculation, weeping, exudation, erythema, and edema. During the subacute state, macroscopic vesiculation and weeping may or may not be present; there is less erythema and edema. Scaling and lichenification occur later. In this paper no distinction will be made between the terms eczema and dermatitis.

Mechanisms of Dermatitis of the Hands

Many mechanisms provoke eczematous eruptions of the hands (physical agents; contact with primary irritants and sensitizers; infection with viruses, bacteria and fungi; tension, fatigue, and heredity).

Physical Agents

Trauma, friction, excoriation, heat, cold, moisture, maceration, and radiation (actinic, roentgen or radium) may produce dermatitis of the hands. The effect of these agents includes lacerations, bruises, crushing injuries, chapping, burns, frost bites, sunburn, and radiodermatitis. A prerequisite



Figure—Contact dermatitis of the hands due to exposure to epoxy resin.

for the successful management is the elimination of continued action of the irritants and protection by means of bland, soothing applications which allow the skin to heal as best it can. In some cases of radiodermatitis, plastic surgery is necessary.

Primary Irritants and Sensitizers

Causative agents in this group are too numerous to list. They include occupational and industrial excitants; substances encountered in hobbies, games, professions; soaps, cleansers, plants, gloves, rings, bracelets, topical medications applied to self or others; in fact all objects which may be touched, handled, held or worn. The irritant and drying effects of soaps and detergents, especially during the winter months, may initiate an eczematous eruption of the hands. Common household substances (bleaches, waxes, polishes, hand lotions and creams) may add to the irritation. Secondary infection may occur.

Parasitic Infections

External infections include impetigo, infectious eczematoid dermatitis, and dermatophytosis. Many others (warts, carbuncles, cutaneous diphtheria, anthrax, tuberculosis, and syphilis) will not be considered in this presentation.

Primary fungous infection of the hands is rare. Demonstration of the organism by direct potassium hydroxide mounts, examined microscopically or by cultures on Sabouraud's medium, is necessary for diagnosis.

The role of internal focal parasitic infections in the production of eczematous eruptions on the hands is debatable. Undoubtedly, significant foci may exist in distant sites from cutaneous diseases such as teeth, gums, tonsils, sinuses, prostate, cervix, bladder, and the gastrointestinal tract.

Tension and Fatigue

Exudative neurodermatitis (nummular eczema) is a distinct type of chronic dermatitis of the hands. The disorder attacks the dorsal surfaces and other parts of the extremities. There are oval patches, 1 to 5 cm in diameter, consisting of groups of vesicles or vesicopapules. The lesions are sharply demarcated, worse in winter and aggravated by friction, soaps and detergents. In many cases the dermatosis is recalcitrant to treatment (roentgenotherapy, sulfonamides, antibiotics, removal of foci of infection, and steroids).

Lichen Chronicus Simplex

Circumscribed neurodermatitis of the palms and soles may resemble keratoderma climactericum but does not occur exclusively in women. The patients are adults, the majority of them beyond middle age. The lesions consist of sharply circumscribed, hyperkeratotic, nonvesicular plaques, which are intensely itchy and frequently become fissured. Symmetry is the rule. The lesions are usually located on the mid-palmar regions, although occasionally on the fingers.

Atopic dermatitis, a disorder of unknown cause, is usually flexural but may affect the hands predominantly. It is a dry disease unless it is secondarily infected. It usually occurs on the dorsal surfaces of the hands and fingers, tends to become worse during the winter months, and is resistant to treatment. Heredity, tension, and fatigue play a poorly understood role.

Management of Dermatitis of the Hands

The treatment of dermatitis of the hands requires both internal and external measures. Although internal medications have assumed increased importance during the past few years, topical therapy is still important.

Old remedies such as antipruritics (menthol, camphor, and phenol), keratoplastics (salicylic acid and resorcin in weak concentration), keratolytics (the same drugs in stronger concentration), and anti-eczematous agents (Ichthyol, Naftalan, various types of tar, Vioform, and Sterosan) have been replaced largely by hydrocortisone and other steroids. Secondarily-infected eczematous eruptions of the hands are benefited by the application of a steroid in combination with one or more of the antibiotics such as bacitracin, neomycin and polymyxin.

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Medicine Today

Probably the ideal of the modern doctor is Sir William Osler, a Canadian who studied in Germany and taught in the United States and England. By moving about briskly, he kept himself in fine trim, all but his mustache.

Osler, a great practical joker, proved that you needn't be serious to be a successful physician. Once he called up a man named Smith and asked if he would come to lunch to meet Jones. He explained to Smith that Jones was quite deaf. Then he called up Jones and asked him to come to lunch to meet Smith, explaining that Smith was quite deaf. At lunch, Smith and Jones, both of whom had excellent hearing, leaned forward and yelled at each other, and Osler roared with laughter. When they discovered the joke that had been played on them, it's a wonder they didn't box Osler's ears. Then he might have needed the services of an ear specialist himself.

Osler's picture hangs in the office of many a physician, as a reminder of how lucky one is not to have to wear a high stiff collar like that. And Osler's textbook, The Principles and Practice of Medicine, is the Bible of young doctors who are too busy to go to church.*

*Richard Armour: It All Started with Hippocrates, 1966.

The First Patients

In a cave in France a Neanderthal man lay carefully buried; he was between forty and fifty years old when he died, an advanced age at a time when few lived beyond thirty years; he was crippled by arthritis and all but toothless. For years before his death, he must have been increasingly helpless; he could not have survived unless his people had tended him, brought him food, perhaps even chewed it for him.

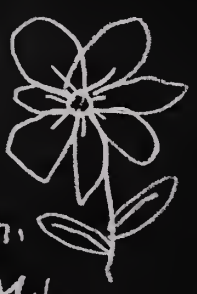
In a cave in Iraq seven Neanderthalians were killed accidentally when the roof of their cave collapsed. One was an infant. Of the six adults, one was arthritic, and had also been wounded in the side, probably by a spear. Another had a severe birth defect; his right arm was useless and he may have had only one eye; his crippled arm had been amputated above the elbow at some earlier time, the first known case of surgery*

*Felix Marti-Ibanez, M.D.: The Patient's Progress, 1962.

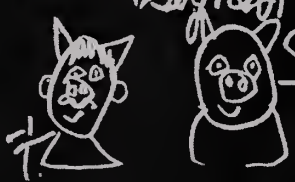
Editor's Note: I am sure that man of the human species has always buried his dead; but I have doubts that in those days they ever pureed their food for their invalids by any method.

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William Mahoney

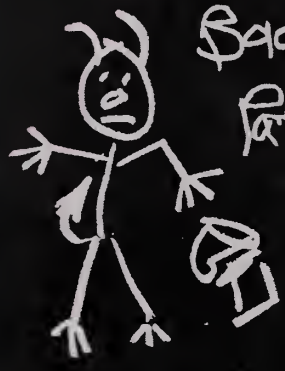


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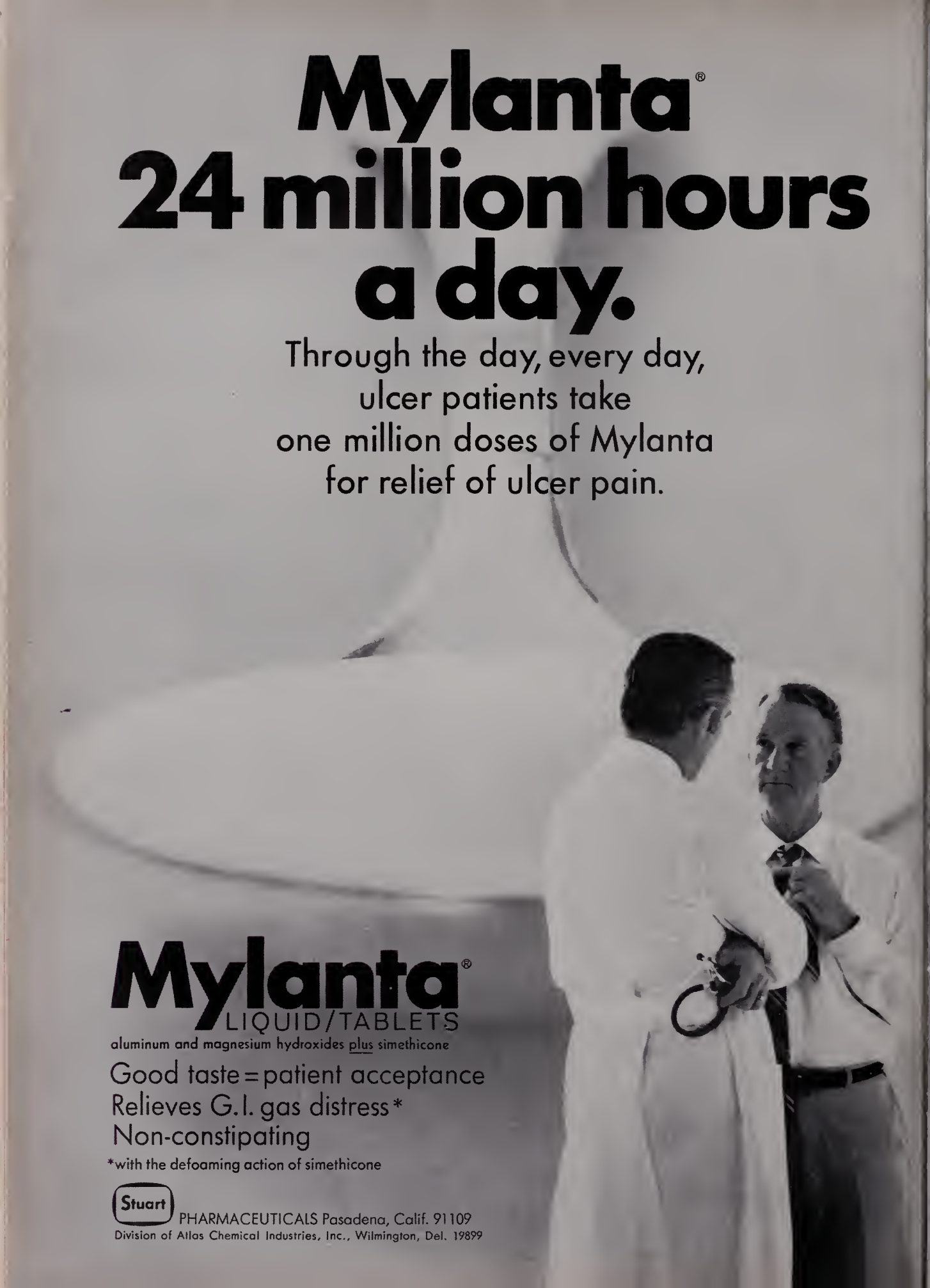
References: (1) Sands, R. X.: New York St. J. Med. 61:2598-2602, 1961; (2) Renner, M. J., et al.: Hosp. Topics 39:71-73, 1961; (3) Haas, Jr., J., and Kay, L. L.: Southwest. Med. 42:30-32, 1961; (4) Marshall, W.: Clin. Med. 7:499-502, 1960; (5) Strauss, B.: Clin. Med. 4:307-310, 1957.

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Special Article

Voluntary Euthanasia

STEVEN SCHJELDAHL*
Cambridge, Massachusetts

For many years in the United States and Great Britain there has been an organized movement to secure the legalization of voluntary euthanasia. Such legislation would make voluntary euthanasia available, in the several states, on demand under specified conditions. The question of voluntary euthanasia is especially relevant today when medicine can prolong the life of many persons indefinitely. Society has always recognized the right of choice in life, but little attention has been given to the right of choice in death.

The various proposals for voluntary euthanasia to end suffering from incurable disease provide that the request be initiated by the person to receive it, that a committee investigate the petition, that a court, upon the recommendation of the committee, consider the issuance of a permit, and that if a permit is granted the act be performed in a hospital by a physician free from criminal and civil liability. Voluntary euthanasia is not an eugenic measure, nor is it an effort toward involuntary population control.

The choice is not between life and death, but between a comfortable and a painful death. Just as in living one has some control over the circumstances of existence, supporters of voluntary euthanasia argue that a person should have control, to the extent possible, over the conditions of his death. At present the only option available is the socially-taboo act of suicide.

The Legal Issues

Voluntary euthanasia if administered by another is homicide by request and hence murder. If euthanasia is self-administered it is deemed suicide. Invitation and consent of the victim neither removes the act from the legal definition of murder nor mitigates the offense. Criminal intent is inferred from the act and, since malice is present in all murders, good motives do not constitute a defense to the charge. Since death is inevitable at some point in time, life expectancy is irrelevant. The very nature of euthanasia implies willfulness and deliberation so as to technically preclude the reduction of a murder charge to manslaughter.

An Accessory

Although there have been no cases, a physician who suggested self euthanasia to a patient, provided a means, or merely gave advice on a means, could be found guilty of murder for assisting a suicide. Besides reflecting an ancient enjoinder against suicide, this law seeks to protect the young, the old, and the disturbed from the undue suggestion and influence of others. Gain may be present in the encouragement of another to destroy himself.

Turning to the legal maze that surrounds a physician indicted for murder (voluntary euthanasia), the discussion must verge on conjecture, as there has been only one physician charged with murder in a situation that could be described as a mercy death. However, in the case of a physician the distinction must be made between inflicting death and allowing death. Direct euthanasia would include such acts as giving a lethal overdose of a drug, pulling the plug on a mechanical device keeping the patient alive, injecting air into the veins and, in general, following any procedure which would accelerate death. Such action must be intentional, for a physician cannot be punished for lack of judgment.† Unless a complaint was filed along with substantial evidence it is very unlikely that criminal charges would be brought against a physician acting in good faith. Not only is prosecution hindered by the

*Graduate Student at Harvard University.

†Arthur Levisohn: Voluntary Mercy Deaths, J. Forensic Medicine, pp 17, April-June, 1961.

problem of detection, but the law respects the integrity of the physician and generally allows him wide latitude in the performance of his professional duties.

The only case of a physician involved in a mercy death that has gone to court is that of Dr. Hermann Sander.

> "In the widely publicized New Hampshire case of State vs. Sander (1950), a physician who dictated into the hospital record a statement that he had injected ten cubic centimeters of air four times into the veins of an incurably ill, suffering patient, and that 'she expired within ten minutes after this started,' was acquitted by a jury of charges that he murdered 'in an act of mercy,' on the ground that there was no sufficient proof of causation."*

Dr. Sander pleaded temporary insanity as a defense to the charge. However, an inquiry to Professor Arthur Hertig of Harvard Medical School regarding this alleged case of euthanasia reveals that the victim was already dead when Dr. Sander injected air into her veins.

> ". . . Mrs. Borota, who was alleged to have been a case of euthanasia, died at the Hillsboro Hospital (New Hampshire), allegedly from having air injected into her vein. It was shown by the pathologist from the Department of Legal Medicine (Harvard) that the vein alleged to have been injected was indeed closed off by intravascularly clotted blood (thrombi). Moreover, there was very little air in the patient's vascular system. She undoubtedly died of extensive cancer."†

Thus the conclusion is that there have been no prosecutions in the United States of a physician for actually administering euthanasia.

Indirect Voluntary Euthanasia

The legal problems raised by indirect forms of voluntary euthanasia are intricate. Withholding necessary and indicated medication or treatment, discontinuing medical therapy, or failure to apply known and standard procedures would constitute indirect euthanasia. Such inaction, if deliberate and intended to produce the death of the patient, would be murder. It is a legal principle that if there is a duty to act, then an omission to act is the same as a positive act, and a physician who simply "let the patient die" would bear the same criminal liability as one who performed a direct act of euthanasia.

In addition to criminal charges a physician may incur civil liability for failure to act, and the courts could construe the failure to act as grossly improper treatment (malpractice). An upset family not wishing the patient to die may accuse the physician of negligence in the patient's death. As a precaution even physicians, upon agreement, who "let the patient go" may pretend to still be giving treatment. Often it is very difficult to determine exactly what inaction accelerated or caused death.

Surreptitious Act

In the attitudes of the medical profession toward voluntary euthanasia a profound ambiguity exists between expressed policies and actual practice. Few doctors prolong needless suffering. While society requires nominal subscription to the rules which forbid the practice of voluntary euthanasia, the physician who acts surreptitiously is almost immune from prosecution. Indeed, a physician would be thought unfeeling if he did not follow the invisible medical practice of diminishing suffering in hopeless cases even to the point of speeding along impending death.‡

Philosophical

Otto Guttentag, M.D., professor of medical philosophy at the University of California Medical School in San Francisco, writes:

> "If we understand by euthanasia the intentional acceleration of the approach of death, I could visualize some situations in which one might contemplate such a procedure. Hence one probably should differentiate between acts of omission and acts of commission since the former are more a medical problem than the latter. Concerning acts of omission: (the request) 'please let me die in peace, my time has come; don't keep me going with all the techniques at your disposal;' I could, as a doctor, visualize myself complying with his wish."#

---

*Helen Silving: Euthanasia. Univ Penn Law Rev, pp. 353, December, 1954.

†Personal communication (November 6, 1967) from Arthur Hertig, M.D., Professor of Pathological Anatomy, Harvard Medical School.

‡According to Levisohn, ibid., an informal poll of 250 Chicago physicians in 1961 revealed that 61% of those questioned actually practiced euthanasia in instances of incurable adult sufferers. Dr. Levisohn is professor of medical jurisprudence at the Chicago Medical School. A *New Medical Materia* survey in 1962 disclosed that of those physicians polled, 31% felt euthanasia justified when the patient is in great pain without hope of recovery.

Personal communication (January 3, 1968) from Otto Guttentag, M.D., Professor of Medical Philosophy, University of California at San Francisco.

It seems, however, that the assumption that all or very many persons beg for quick release in their final illness is erroneous. The actual demand for voluntary euthanasia appears to be minimal. Professor B. J. Kennedy of the University of Minnesota writes:

> ". . . in our hospital and in my experience, the question of euthanasia is a very rare problem. I do not believe cancer patients request termination of their lives."*

And Dr. William McConahey of the Mayo Clinic writes:

> ". . . among the many hundreds of terminally ill patients whom I have cared for through their final illness and until death, not one has asked me to do something to end his life early. . . ."†

Intractable or Incurable

Not only are diagnosis and prognosis subject to error, but even with correct diagnosis the prognosis may be inaccurate. There are inoperable carcinomas which inexplicably cease to grow, and there are accident victims who survive against impossible odds. There is always the chance that the physician may confuse the intractable with the incurable case, and often it is hard to determine with much certainty the signs of impending death. It is sometimes said that patients die because the physician thinks they must. Likewise, by "shooting the works" the patient may be inadvertently improved or cured.

Psychological

Approached from the psychological perspective the wish for release from suffering through euthanasia and a physician's willingness to administer it appear rather different. K. R. Eissler writes:

> "Euthanasia is not always born out of charity but may mean to the physician's unconscious the gratification of a murderous impulse."‡

He adds that some physicians may wish a patient dead because they are tired of the burden of treating him, or because the patient arouses their own anxiety about suffering and death. Further, the patient's request for euthanasia may be an atonement for guilt over illness. A plea for euthanasia can mask a severe depression amenable to treatment. It can be a covert attempt to control or punish others by the threat of dying immediately.

Medical and Economic Burden

It is important to note that proposed euthanasia legislation is designed to apply only to those persons capable of making a voluntary rational decision. It has been contended that this stipulation overlooks the more critical problem of maintaining indefinitely the comatose who constitute a major medical and economic burden. These people may live for many months, needing extraordinary treatment at high cost without hope of regaining consciousness. Whether extraordinary measures should be used to keep a person with massive, irreversible brain damage alive, or be withdrawn when death is sure to follow, constitutes a real dilemma. Henry K. Beecher of Harvard Medical School suggests:

> "The unconscious patient with overwhelming brain damage can be maintained only by extraordinary means. When it becomes evident that the brain is dead, there is an obligation to discontinue extraordinary supports."#

Legislative Endeavors

Today debate on euthanasia centers on the relative merits of prolonging life and actively prolonging the process of dying. Lord Horder, physician to King George V, cogently said:

> ". . . the good doctor is aware of the difference between prolonging life and prolonging the act of dying."¶

Most physicians do differentiate between extraordinary and ordinary means of preserving life. If death becomes certain and intolerable pain persists there is an obligation not to prolong the patient's agony. There is no treatment for death.

The euthanasia societies of the United States and Great Britain have been active in promot-

*Personal communication (November 6, 1967) from B. J. Kennedy, M.D., Professor of Medicine, University of Minnesota.

†Personal communication (November 6, 1967) from William McConahey, M.D., Mayo Clinic, Rochester, Minnesota.

‡K. R. Eissler: The Psychiatrist and the Dying Patient, pp. 118, New York, 1955.

#At page 4, Henry K. Beecher: The Right To Die. Harvard Crimson, pp. 4, December 19, 1967.

¶Lord Horder: Signs and Symptoms of Impending Death. Practitioner, pp. 337, August, 1948.

ing legislation designed to legalize the practice. The Voluntary Euthanasia Society in England was headed by Lord Moynihan, President of the Royal College of Surgeons, and as a result of the efforts of the Society in 1936 a bill was introduced into the Lords but was lost. Again in 1950 it was moved in Lords that the matter be inquired into, but the motion was lost. In the United States a bill was introduced in the Nebraska legislature in 1937 to legalize euthanasia but was lost in committee. In 1947 a similar bill was lost in the legislature of the State of New York.

In conclusion then it seems appropriate to address the question of whether voluntary euthanasia ought to be legalized. The law is a didactic instrument in American society, regulating social behavior. The law influences the development of institutions and provides a model toward which action conforms. The law is flexible and sensitive to social change, and at the same time it tends to minimize conflict and maintain equilibrium within the social system. In an era of astounding technological progress law and ethics must combine to insure the moral application of science. Medical sophistication makes it possible to prolong life through mechanical means for an indeterminate period. The application of this skill is of supreme importance for the welfare of society. Used without judgment and adopted as an end in itself, technically-produced human longevity may be disastrous, for the law of diminishing returns will eventually begin to operate. While it is often possible to preserve the biological organism for a long period, death is more than a biological event, for life is more than chemical metabolism. Essential to life is the concept of personality, and when the "person" has died, a responsibility exists *not* to prolong the eventual demise of the organism.

References may be secured from the author.

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The evidence was sufficient to support the finding that the manufacturer was negligent in failing to warn users of the scalding temperatures of the water in the jar. The court ordered judgment entered on the jury's verdict for the child in the amount of $150,000.

Case Reference: McCormack v. Hankscraft Company, Inc., 154 N.W. 2d 488 (Minn., Nov. 17, 1967; rehearing denied, Dec. 12, 1967).
The Citation—Vol. 17; No. 2, May 1, 1968.

Occasions do not make a man either strong or weak, but they show what he is.
—Thomas A. Kempis

To my embarrassment I was born in bed with a lady.—Wilson Mizner

Diligence is the mother of good luck.—Franklin.



Well, Dr. Cunningham! I was just telling Herbert I should talk to you about my allergy. First my nose starts to tickle and..."

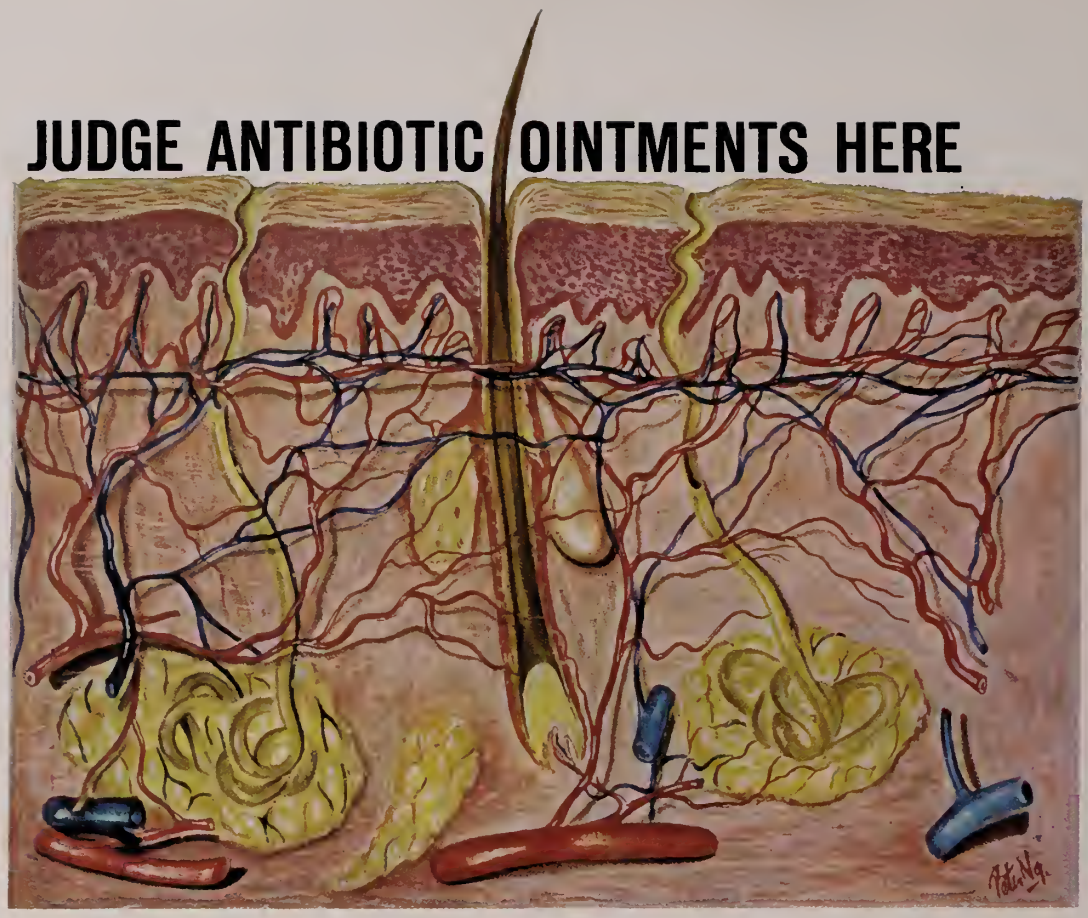
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1. Kannel, W.B., *et al.*: *Circulation* 35:734, 1967.
2. Thomas, H.E., Jr., *et al.*: *Med. Times* 95:1099, 1967.
3. Albrink, M.J., in: Beeson, P.B. & McDermott, W. (eds.): *Cecil-Loeb Textbook of Medicine*, ed. 12, Phila.: W.B. Saunders Co., 1967.

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"Oh doctor. How wonderful," she gushed. "But when? Before or after?"

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*Mark Wachs

Vital Point

"Now," soothed the psychiatrist, "tell me about this dream you had."

"Well," said his feminine patient, "I dreamed I was walking down the street with nothing on but a hat."

"And were you embarrassed?"

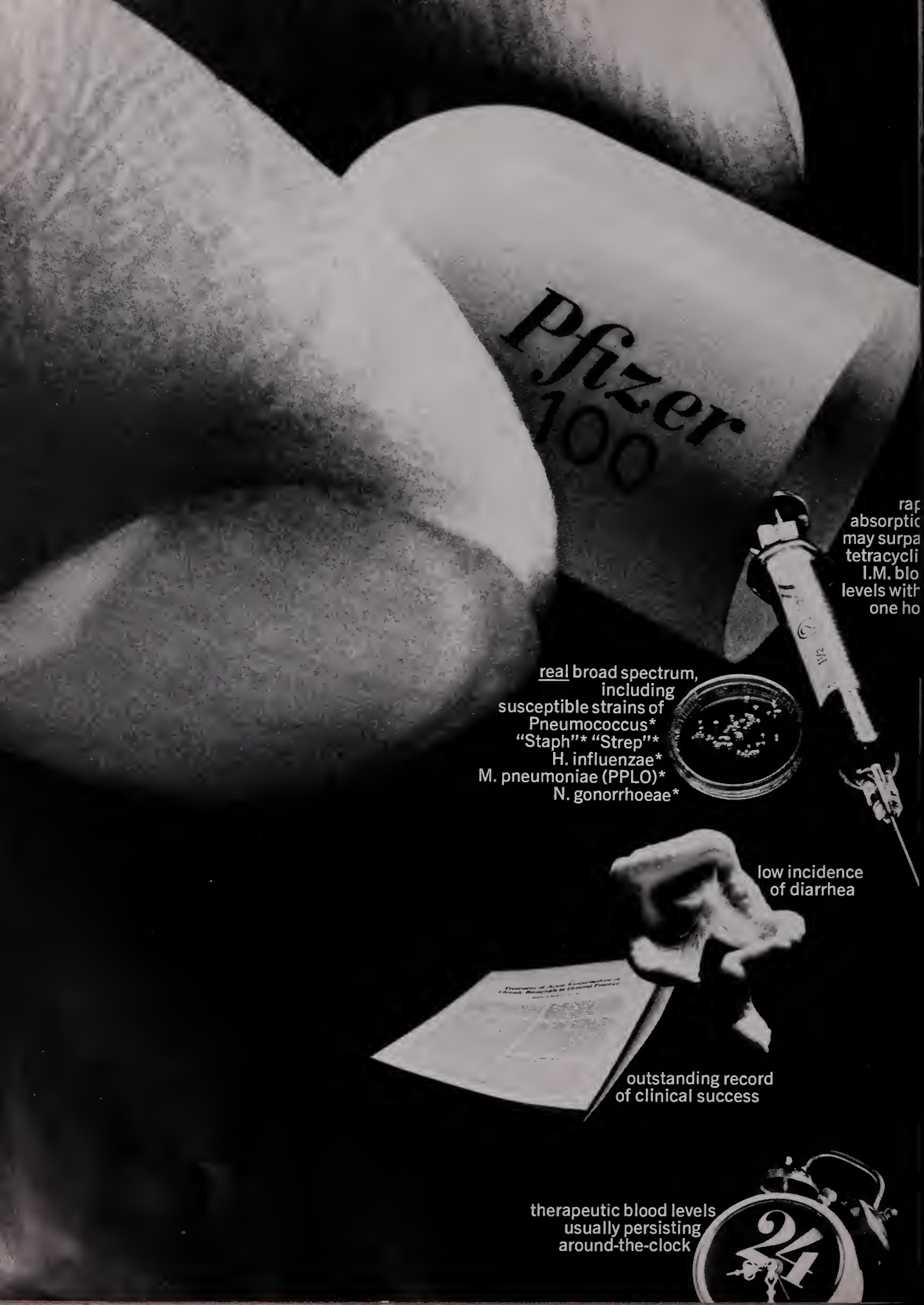
"Yes, I was. It was last year's hat."*

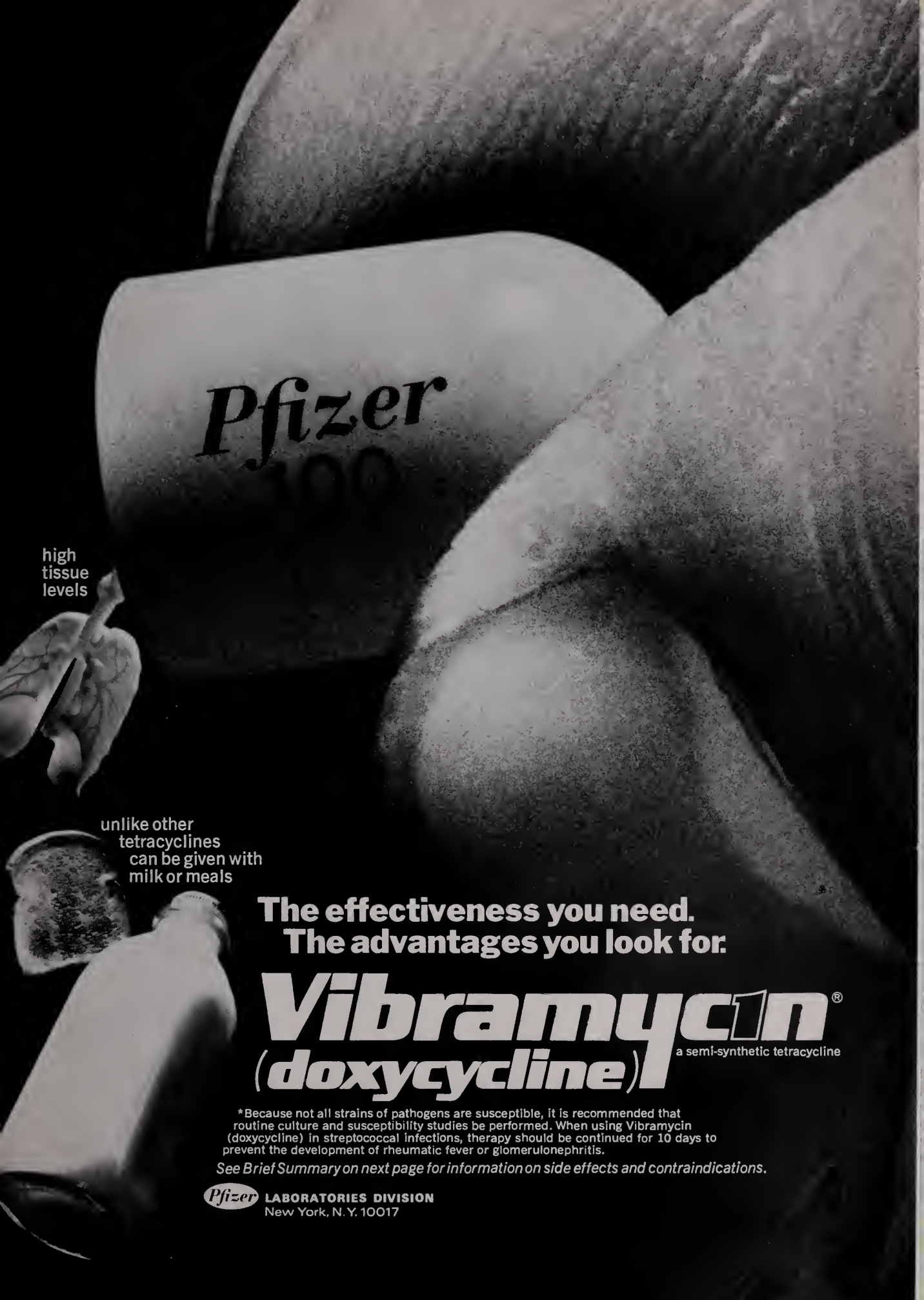
*The Speaker's Handbook of Humor, Maxwell Droke.

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a semi-synthetic tetracycline

*Because not all strains of pathogens are susceptible, it is recommended that routine culture and susceptibility studies be performed. When using Vibramycin (doxycycline) in streptococcal infections, therapy should be continued for 10 days to prevent the development of rheumatic fever or glomerulonephritis.

See Brief Summary on next page for information on side effects and contraindications.

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And for added convenience in the hospital pharmacy, Vibramycin is available in unit-dose packs of 100 (10 x 10's) for both the 100 mg. and the 50 mg. capsules.

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BRIEF SUMMARY

Contraindicated: In individuals who have shown hypersensitivity to doxycyciine.

Warnings: The usual dosage and frequency of administration of Vibramycin (doxycycline) differs from those of other tetracyclines. Exceeding the recommended dosage may result in an increased incidence of side effects.

If renal impairment exists, even usual doses may lead to excessive accumulation of the drug and possible hepatic toxicity. For such patients, lower than usual doses are indicated and, if treatment is prolonged, Vibramycin serum level determinations may be advisable.

Vibramycin, like other tetracyclines, may form a stable calcium complex in any bone-forming tissue, although *in vitro* Vibramycin binds calcium less strongly than other tetracyclines. The use of Vibramycin during tooth development (last trimester of pregnancy, neonatal period, and early childhood) may cause discoloration of the teeth (yellow-gray-brownish). This effect may occur mostly during long-term use, but also may occur with short-treatment courses.

Increased intracranial pressure with bulging fontanelles has been observed in infants receiving tetracyclines. This effect has disappeared rapidly on cessation of therapy with no sequelae.

In certain hypersensitive individuals treated with Vibramycin, exposure to direct sunlight may precipitate a photodynamic reaction. In individuals with a history of photoallergic reactions to tetracyclines, exposure to direct sunlight should be avoided and treatment should be discontinued at first evidence of skin discomfort.

Precautions: As with any antibiotic, overgrowth of nonsusceptible organisms may occasionally occur. Constant observation of the patient is essential. If such superinfections are encountered, Vibramycin should be discontinued and replaced by appropriate therapy.

When treating gonorrhea in which lesions of primary or secondary syphilis are suspected, proper diagnostic procedures, including dark-field examinations, should be utilized. In all cases in which concomitant syphilis is suspected, monthly serological tests should be made for at least four months.

Adverse Reactions: Nausea, vomiting, diarrhea, vaginitis, as well as reactions of an allergic nature such as dermatitis, urticaria, and anaphylaxis may occur but are rare. Glossitis, stomatitis, proctitis, onycholysis and discoloration of the nails may rarely occur during tetracycline therapy as with other antibiotics. If severe adverse reactions, individual idiosyncrasy, or allergy occur, discontinue medication.

As with other tetracyclines, elevation of SGOT or SGPT values, or elevated BUN have been reported, the significance of which is not known at this time. Anemia, neutropenia, and eosinophilia have been reported, as with other tetracyclines.

Animal Pharmacology: As with other tetracyclines, at doses greater than those recommended for human usage, Vibramycin produces discoloration of animal thyroid glands. Careful monitoring of animals and humans has disclosed no abnormalities of thyroid function studies. Also, as with other tetracyclines, at relatively high oral doses, evidence of hepatotoxicity has been noted in dogs and signs of gastrointestinal intolerance have been seen in both dogs and monkeys.

Dosage: The usual dose of Vibramycin is 200 mg. on the first day of treatment (administered 100 mg. every 12 hours) followed by a maintenance dose of 100 mg./day. The maintenance dose may be administered as a single dose, or as 50 mg. every 12 hours. In the management of more severe infections (particularly chronic infections of the urinary tract), 100 mg. every 12 hours is recommended. The recommended dosage schedule for children weighing 100 pounds or less is 2 mg./lb. of body weight divided into two doses on the first day of treatment, followed by 1 mg./lb. of body weight given as a single daily dose or divided into two doses, on subsequent days. For more severe infections up to 2 mg./lb. of body weight may be used. For children over 100 lbs. the usual adult dose should be used.

Acute gonococcal anterior urethritis in males —a single dose of 300 mg. or 100 mg. b.i.d. for 2-4 days.

Acute gonococcal infections in the adult femal should be treated with doses of 100 mg. b.i.d. until cure is effected.

Therapy should be continued beyond the time that symptoms and fever have subsided. When used in streptococcal infections, therapy should be continued for 10 days to prevent the development of rheumatic fever or glomerulonephritis.

If gastric irritation occurs, it is recommended that Vibramycin be given with food or milk. Studies indicate that the absorption of Vibramycin is not markedly influenced by simultaneous ingestion of food or milk.

Simultaneous administration of aluminum hydroxide gel given with tetracycline antibiotics including Vibramycin has been shown to decrease absorption.

Supply: Vibramycin Hyclate (doxycycline hyclate) is available as capsules containing doxycycline hyclate equivalent to 50 mg. of doxycycline, bottles of 50, unit-dose pack of 100 (10 x 10's), and X pack of 50 (5 x 10's); capsules containing doxycycline hyclate equivalent to 100 mg. of doxycycline, bottles of 50, unit-dose pack of 100 (10 x 10's), and V pack of 25 (5 x 5's).

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More detailed professional information available on request.

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(doxycycline)
a semi-synthetic tetracycline

Humanities

"O, Mon Pylore!"

The post-mortem examination of Napoleon's body was performed by Francesco Antommarchi, a young Corsican physician, anatomist, and pathologist, who was sent to St. Helena about eighteen months before Napoleon's death in the hope that he, being a Corsican, would be able to win the Emperor's confidence and cure the illness of which he was already complaining. Napoleon used to suffer from severe pains in his stomach; he would clasp himself, and groan, "O, mon pylore!" By that time he was suffering from cancer of the stomach, and Antommarchi did not suspect it. When Napoleon groaned and writhed in agony it is said that Antommarchi merely laughed, and prescribed him tarter emetic in lemonade.

Though truthfulness was not a strong point with Antommarchi, he seems to have known his pathology, and has left us an exceedingly good and well-written report of what he found. Strange to relate, the body was found to be still covered thickly with a superficial layer of fat, and the heart and omenta were also adipose. This would seem impossible in the body of a man who had just died of cancer of the stomach, but is corroborated by a report from a Dr. Henry, who was also present, and is not unknown.

At one point Napoleon's cancerous ulcer had perforated the stomach, and the orifice had been sealed by adhesions. Dr. Henry proudly states that he himself had been able to thrust his finger through it. The liver was large but not diseased; the spleen was large and "full of blood"—probably Antommarchi meant engorged. The intestine was covered by small bright-red patches, evidently showing inflammation of lymphatic tissue such as frequently occurs in general infections of the body. The bladder contained gravel and several definite calculi. There was hardly any secondary cancerous development, except for a few enlarged glands. Antommarchi and the French generally had diagnosed before death that he was suffering from some sort of hepatitis endemic to St. Helena, and the cancer was a great surprise to them—not that it would have mattered much from the point of view of treatment.

Napoleon's hands and feet were extremely small; his skin was white and delicate; his body had feminine characteristics, such as wide hips and narrow shoulders; his reproductive organs were small and apparently atrophied. He is said to have been impotent for some time before he died. There was little hair on the body, and the hair of the head was fine, silky, and sparse. Twenty years later his body was exhumed and taken to France, and Dr. Guillard, who was permitted to make a brief examination, stated that the beard and nails appeared to have grown since death; there was very little sign of decomposition; men who had known him in life recognized his face immediately it was uncovered.

Leonard Guthrie points out that some of these signs seem to indicate a condition of hypo-pituitarism—the opposite to the condition of hyperpituitarism which causes "giantism." Far-fetched as this theory may appear, yet it is possible that there may be something in it.*

*C. MacLaurin: Post Mortems of Mere Mortals, 1925.

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Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms have occurred following abrupt discontinuance. Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation or women of childbearing age, weigh potential benefit against possible hazard.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation, have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

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(1) Siver, R. H.: CMD, 21:109, September 1954. (2) Frykman, H. H.: Minn. Med., 38:19-27, January 1955. (3) McGivney, J.: Tex. State Jour. Med., 51:16-18, January 1955. (4) Quehl, T. M.: Jour. of Florida Acad. Gen. Prac., 15:15-16, October 1965. (5) Weekes, D. J.: NY State Jour. Med., 58:2672-2673, August 1958. (6) Ellis, S. and Spratt, J. S.: JOUR. AMER. GER. SOC., 18:410-415, May 1970.



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Warning: In renal impairment, usual doses may lead to excessive accumulation and liver toxicity. Under such conditions, lower than usual doses are indicated and, if therapy is prolonged, serum level determinations may be advisable. A photodynamic reaction to natural or artificial sunlight has been observed. Small amounts of drug and short exposure may produce an exaggerated sunburn reaction which may range from erythema to severe skin manifestations. In a smaller proportion, photoallergic reactions have been reported. Patients should avoid direct exposure to sunlight and discontinue drug at the first evidence of skin discomfort. Necessary subsequent courses of treatment with tetracyclines should be carefully observed.

Precautions: Overgrowth of nonsusceptible organisms may occur. Constant observation is essential. If new infections appear, appropriate measures should be taken. In infants, increased intracranial pressure with bulging fontanels has been observed. All signs and symptoms have disappeared rapidly upon cessation of treatment.

Side Effects: Gastrointestinal system—anorexia, nausea, vomiting, diarrhea, stomatitis, glossitis, enterocolitis, pruritus ani. Skin—maculopapular and erythematous rashes; a rare case of exfoliative dermatitis has been reported. Photosensitivity; onycholysis and discoloration of the nails (rare). Kidney—rise in BUN, apparently dose-related. Transient, reversible, nephrogenic diabetes insipidus with excessive thirst and polyuria (rare). Hypersensitivity reactions—urticaria, angioneurotic edema, anaphylaxis. Teeth—dental staining (yellow-brown) in children of mothers given this drug during the latter half of pregnancy, and in children given the drug during the neonatal period, infancy and early childhood. Enamel hypoplasia has been seen in a few children. If adverse reaction or idiosyncrasy occurs, discontinue medication and institute appropriate therapy. Demethylchlortetracycline may form a stable calcium complex in any bone-forming tissue with no serious harmful effects reported thus far in humans.

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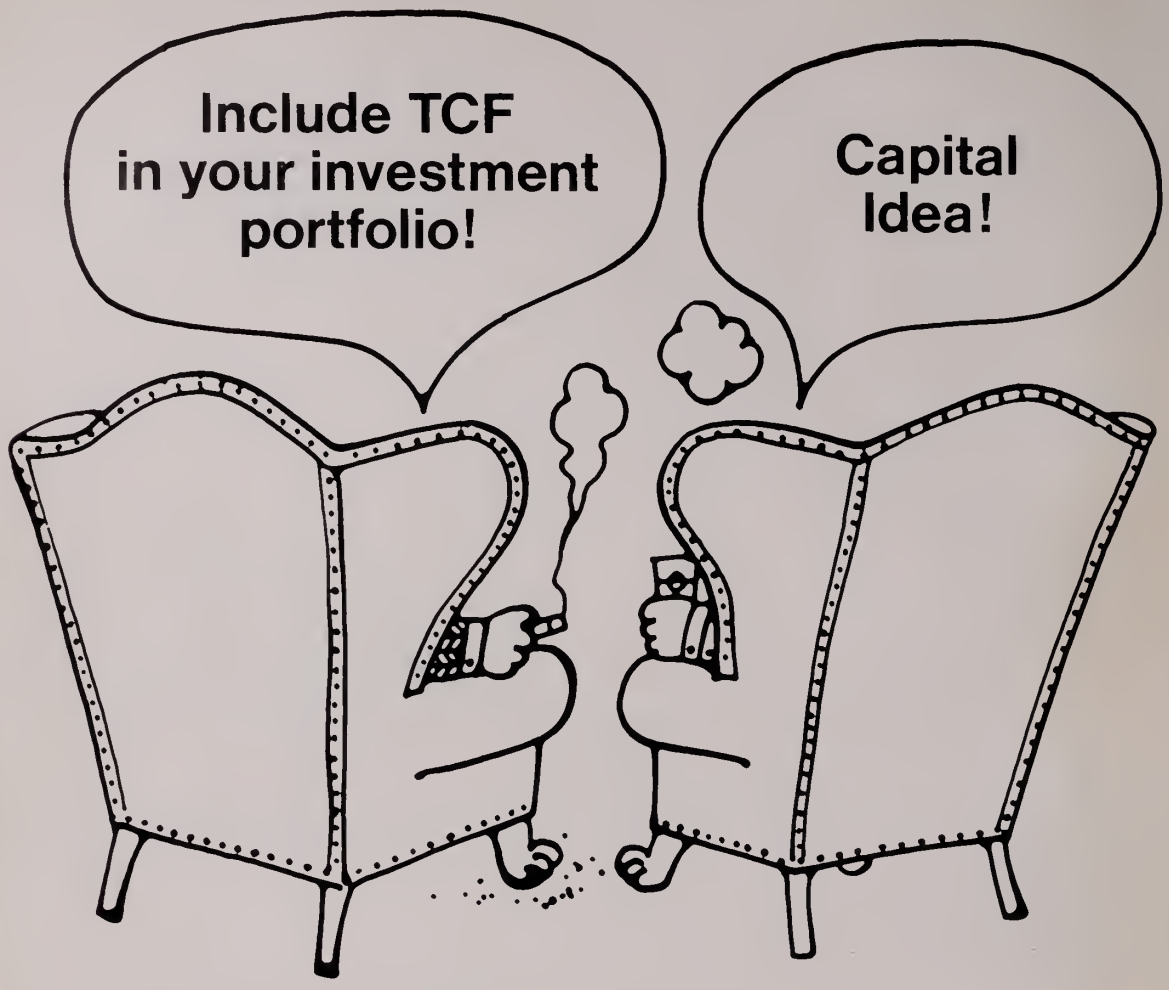
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President's Letter

I KNOW THAT I speak for my fellow psychiatrists in Minnesota as well as for myself when I say that it was a pleasure to see the Minnesota Psychiatric Society listed as one of the organizations now represented by MINNESOTA MEDICINE. It is good to be in such distinguished company and to be the first President of our Society to contribute a letter to this journal.

The American Psychiatric Association was the first national medical association to be organized in the United States. Thirteen hospital physicians founded *The Association of Medical Superintendents of American Institutions* on October 16, 1844. From that inauspicious beginning the American Psychiatric Association had grown to over 16,000 members by the end of the last decade. Nearly all psychiatrists practicing in the United States, as well as several hundred psychiatrists in Canada, Central America and the Caribbean Nations are members of the parent organization. In an effort to increase the efficiency of operation of such a large organization and to stimulate and encourage "grassroots" participation by individual members in the affairs of the American Psychiatric Association, increasing emphasis has been placed on the role played by the various district branches of the parent society.

Psychiatry as a branch of medicine may be considered to have begun with primitive man's attempts to deal with illness by exorcising the malignant evil forces to which he attributed the cause of disease. Until recently, however, the modern psychiatrist has found himself outside of the fraternity of medicine in a position remote or totally isolated from his medical colleagues. Psychiatrists themselves must bear some of the responsibility for this dislocation not only because of their once characteristic passivity, aloofness, and uninvolvement in the mainstream of medicine, but also as a result of the the traditional system of caring for mentally ill patients in large, remote, isolated institutions or asylums. The term alienist was synonymous with psychiatrist during the 19th Century and had an almost prophetic meaning for the psychiatrist with regard to his acceptance as a member of the medical profession by other physicians as well as by the general public.

It would be anachronistic to state that we are about to see a change in the identity of psychiatrists, for the change began in the decade of the 50s in Minnesota and, in many instances, bloomed to fruition during the 60s. The reality of psychiatric units in general hospitals with resulting cooperation and concomitant treatment of patients by psychiatrists, family doctors, and other medical colleagues allows a new image for the psychiatrist, if he is willing and able to earn back his rightful place beside his fellow physicians.

As they move in the direction of rejoining the main stream of medicine, psychiatrists along with other physicians, encounter the expectation by the public that they should be able to meet the increasing needs of a more demanding society. Failure to do so, or to be better understood, means either the threat of bureaucratic control with resulting loss of freedom, or the specter of a continuously tarnished and diminishing public image. As already noted, the traditional model of practice for the psychiatrist in the past was that of the hospital-centered, hospital-employed doctor working in specialized, isolated institutions. It was a kind of socialized model of practice from which the modern psychiatrist has evolved, although today a majority of psychiatrists are found in inde-

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Angina*

Biochemical Explanation

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In 1768 William Heberden at the Royal College of Physicians of London assigned the name angina pectoris to a syndrome of chest pain.[1] Since his account of this disorder has been acclaimed as a classical description, it is worthwhile to reiterate a few passages from his description.

> There is a disorder of the breast marked with strong and peculiar symptoms, considerable for the kind of danger belonging to it, and not extremely rare, of which I do not recollect any mention among medical authors. The seat of and sense of strangling and anxiety with which it is attended may make it not improperly be called angina pectoris. Those who are afflicted with it are seized while they are walking, and more particularly while they walk soon after eating, and with a painful and most disagreeable sensation in the breast, which seems as if it would take their life away, if it were to increase or to continue. The moment they stand still, all this uneasiness vanishes. In all other respects, the patients are at the beginning of this disorder perfectly well and, in particular, have no shortness of breath from which it is totally different.
>
> I have observed something like this affliction in the breast of one woman who was paralytic and have heard one or two young men complain of it in a slight degree, but all the rest whom I have seen, who are at least 20, and were men, and almost all above 50 years old, and most of them with a short neck and inclining to be fat.
>
> The os sterni is usually pointed to as the seat of the malady, but it seems sometimes as if it were under the lower part of it and at other times under the middle or upper part, but always inclining more to the left side, and sometimes there is joined with it pain about the middle of the left arm.

Although William Heberden's power of observation was extremely acute, he was not able to determine the etiology of the pain which he so vividly described, as is evidenced in his next paragraph.

> The pulse is at least sometimes not disturbed by this pain and consequently the heart is not affected by it, which I have had the opportunity of knowing by feeling the pulse during the paroxysm, but I have never had it in my power to see anyone opened who had died of it. The sudden death of the patient's adding so much to the common difficulties of making such an inquiry that most of those with whose cases I have been acquainted were buried before I had heard that they were dead.

Although much has been learned about the etiology of angina, since the time of this description, one must agree that Heberden's description of the pain is concise even by present-day standards.

In 1775 Jenner discussed the morbid changes in the coronary vessels found in the hearts of patients who had complained of angina pectoris prior to their death.[2] Parry, in 1799, clearly described the effects of myocardial ischemia as demonstrated in the morbid anatomy of patients who had suffered with angina pectoris.[2] However, Parry overemphasized the frequency of syncope that is associated with patients who have angina pectoris and, for this reason, many later authors overlooked his significant contribution. Nevertheless, his anatomical descriptions are clear and leave no doubt that he attributed the changes in the gross anatomy of the myocardium to myocardial ischemia. In 1932 Lewis[2] proposed that there was an inconstant state of the coronary vessels and that this was the determining factor in the production of angina.

Muller in 1957 was one of the first to study the syndrome of angina with cardiac catheterization.[3] Patients with a right heart catheter were exercised to the point of inducing an anginal attack. From these studies he found that there was a rise in pulmonary artery pressure and also in pulmonary capillary pressure associated with the development of angina which showed electrocardiographic changes. In

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1962 Ross[4] noted a rise in the left ventricular end-diastolic pressure in two patients immediately prior to an anginal attack which had also been induced by exercise. In 1965 Cohen,[5] in Gorlin's laboratory, similarly induced anginal attacks in patients and found: (1) a decreased ejection rate of the left ventricle, (2) a decreased stroke volume, (3) a decreased cardiac output, all associated with a normal ejection time and a normal rate. However, he was not able to confirm the rise in pulmonary artery pressure and a rise in pulmonary capillary pressure reported by Muller.

Meanwhile, in 1918, Bousfield described electrocardiographic changes in patients suffering from an attack of angina, and in 1928 Feil and Seigel[6] stated that the electrocardiographic changes associated with anginal attacks were due to transient vascular changes.

Myocardial Neuronal Transmission of Pain

Sensory Fibers

At least two types of sensory fibers can be found in the myocardial muscle. Fibers either emanate from a perivascular network encircling the coronary arteries or from a perivascular network running parallel to the coronary vessels. This latter set of fibers terminate in free-branching, unmyelinated, non-specific nerve endings and are thought to be associated with the transmission of pain from the myocardial muscle.[7] They are predominantly the C type fibers.* Figure 1 depicts these fibers and demonstrates current thinking as to what initiates the pain at the nerve ending.

By-products of Ischemic Muscle

By-products resulting from the ischemic muscle become activated and then stimulate these C fiber nerve endings. With elevated potassium ion and elevated hydrogen ion in the interstitium, which is conceiveable in conjunction with anaerobic metabolism, these activated by-products may more strongly stimulate the nerve fibers. The impulses passing along the fibers are then brought up to the level

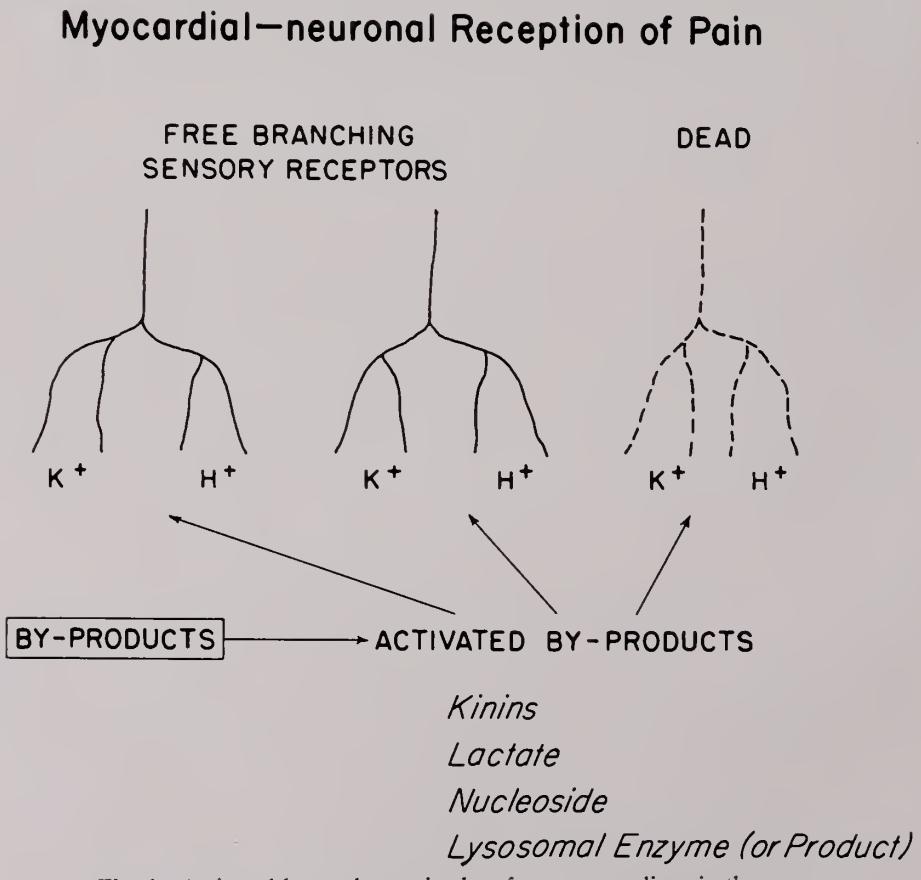


Fig. 1—Activated by-products stimulate free nerve endings in the presence of elevated local concentrations of potassium and hydrogen ions. (Modified from Gorlin.[7])

of the eighth cervical and the first four thoracic ganglia, and are then directed up the lateral spinal thalamic tracts until they reach the level of the thalamus from which they are projected into the cortical level of the brain.

Alterations of Pain Stimuli

With variations in the concentration of the activated by-products as well as hydrogen ion and potassium ion at the level of the nerve endings, it follows that not all anginal attacks produce the same amount of pain. These variations in the ratios of these ions with the same concentration of chemical mediators (by-products) may result in variable stimulation of nerve fibers.

Death of Nerve Fiber

Figure 1 also indicates that if there is death of a nerve fiber, this fiber is no longer able to transmit pain, and perhaps this is the clinical situation which exists when there is a decrease in the anginal attacks following myocardial infarction in a patient.

Other Processes

Furthermore, the impulses coming from the pain fibers in the myocardium utilize the same pathways as impulses which are directed into the cortical level from other organ systems. Gorlin has stated that he feels that all patients with uncontrollable angina have a disease process existing other than coronary artery disease[7]: an *active hiatal hernia, a peptic ulcer, pancreatitis, biliary calculi,* or some other abdominal problem. He further states that after these abdominal problems have been corrected, the patients are then able to control their angina by the usual methods. In addition to potentiating the impulses which have already been generated from the myocardium, it may be that with this segmental overflow along the ganglionic chain and the lateral pathways, experiences which do not generate conditions necessary for angina may produce anginal pain in the presence of these other diseases.

In addition, there is a re-interpretation of the information when it reaches the cortical level of the brain, so that under some conditions a patient *may not perceive pain if he is engrossed in a certain type of activity.* A man attempting to shave in the morning in a bathroom which is being overrun by children may experience angina despite the fact that he is performing very little activity. However, his running after a streetcar while going to work may result in the expenditure of a great deal more energy but may not be associated with the perception of any anginal pain. There are some who believe that under some circumstances angina may be a *conditioned reflex* and result from a neuropsychiatric response.

Myocardial Metabolism

Aerobic Enzymes

There are various indications that myocardial metabolism is almost totally aerobic. The myocardium has a very high concentration of aerobic enzymes, but a very low concentration of anaerobic enzymes. Furthermore, the mitochondria, of which there are many in the myocardium, possess very large cristae which have

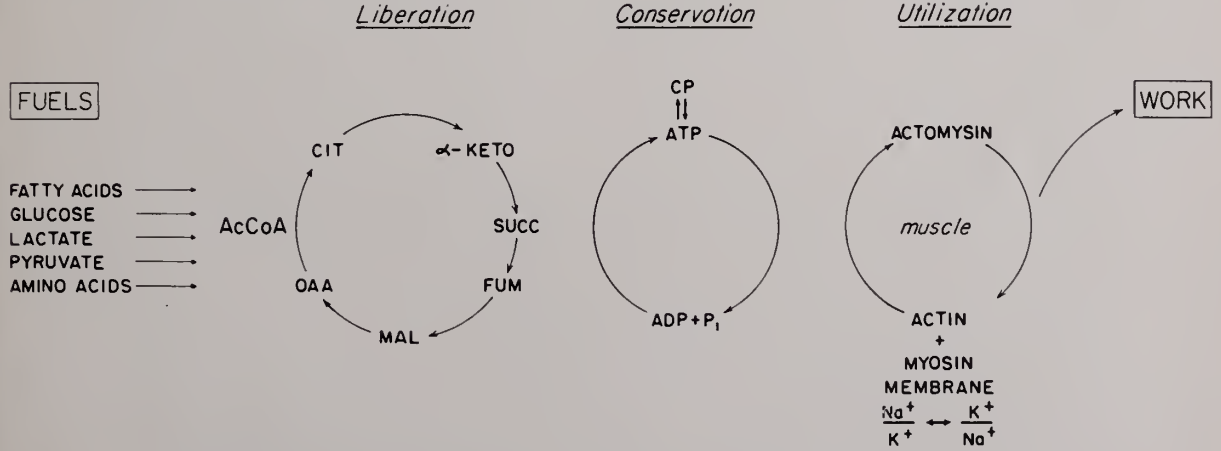


Fig. 2—Stages of energy brought to myocardium. (Modified from Clinical Disorders of the Heart Beat.[8])

been accepted as an indication of high levels of oxidative phosphorylation.

Compounds which enter the myocardial cell as fuel are broken down to liberate their chemical energy which, in turn, passes through various stages as shown in Figure 2. Energy is generally liberated from the carbon-carbon and carbon-hydrogen bonds.

Fatty Acids and Carbohydrate

In a fasting state, energy is generally liberated from the carbon-carbon and carbon-hydrogen bonds. Although some energy is liberated from carbon-nitrogen and nitrogen-oxygen bonds, as well as from carbon-sulphur and sulphur-hydrogen bonds, these represent a small amount of energy gained by the myocardium when compared to the first two mentioned bonding types. In a fasting state the myocardium will preferentially metabolize free fatty acids which make up about 60 to 65 percent of the total energy expended; carbohydrates on the other hand make up approximately 30 or 35 percent of the energy used by the heart. This ratio may be reversed, however, by the intravenous infusion of large amounts of carbohydrate in the form of glucose.

Stored Energy

Of significance in myocardial metabolism is the uptake of *lactate* from the coronary arteries with its subsequent utilization resulting in a lower lactate level in the coronary venous blood. *Amino acids,* which may also be taken up by the myocardium, can be deaminated and provide energy by entering the tricarboxylic acid cycle at the oxaloacetic or alpha-ketoglutarate level. The high energy bonds which result from the breakdown of fat, carbohydrate and amino acids are conserved in the myocardium and stored in the form of adenosine triphosphate as well as creatinine phosphate. The stored energy is subsequently utilized in the contraction of the myocardium as well as in the maintenance of the normal ionic gradients across the cell membranes.

The aerobic metabolism of the myocardial cell is depicted in Figure 3. Here the fatty

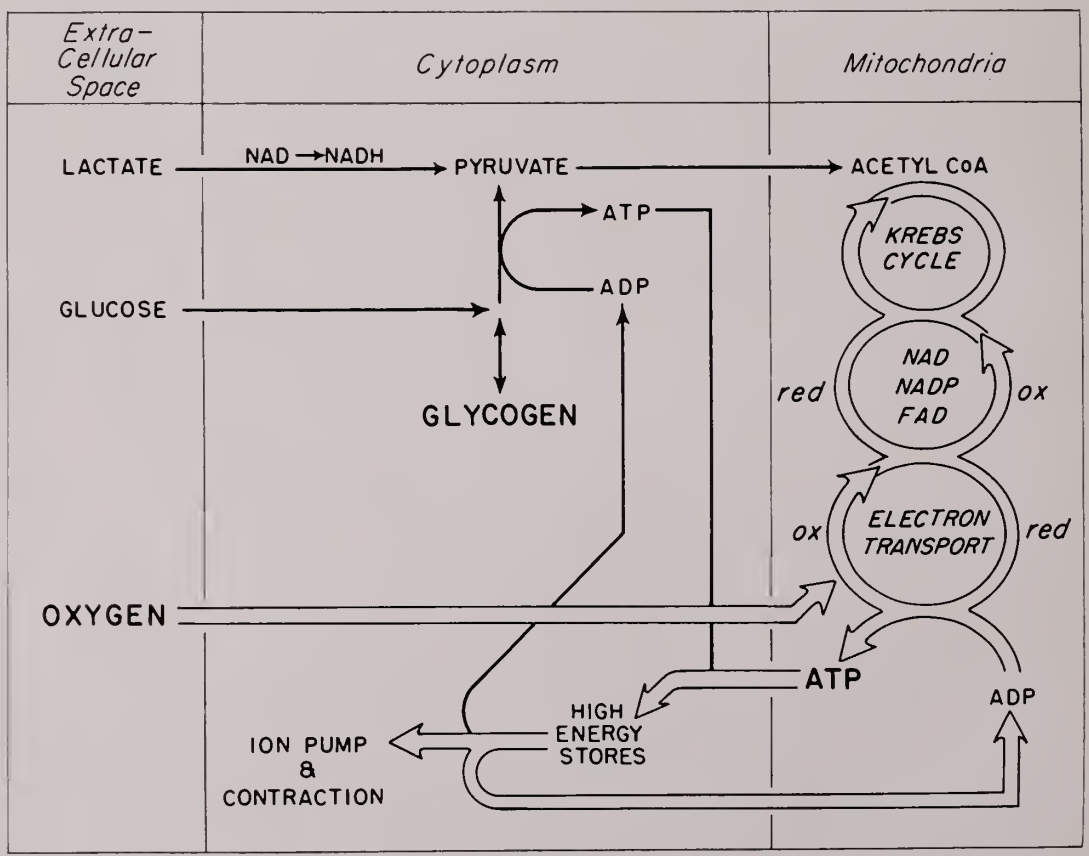


Fig. 3—Outline of aerobic metabolism of myocardial cell.

acids which enter the cell may be stored as myocardial lipid when the amount of substrate uptake is greater than the amount of energy being utilized by the myocardium.

*The Kreb's Cycle**

The *free fatty acids* can also be broken down into two carbon fragments from which they can enter into the Kreb's cycle. Lactate which enters the cell is oxidized as nicotinamide adenine dinucleotide is converted to nicotinamide adenine dinucleotide dehydrogenase, and the pyruvate which is formed may be converted into a two-carbon fragment which subsequently enters the Kreb's cycle. Glucose entering the cell may be converted into *glycogen as a storage* product under conditions utilizing less energy; or it may be converted into two molecules of pyruvate with the production of two high-energy phosphate bonds through the anaerobic breakdown of glucose in the cytoplasm. *Amino acids* which are taken into the cell may be utilized for the building of newer protein moieties or broken down to enter the Kreb's cycle. Oxygen which enters the cytoplasm of the cell is directed into the mitochondria where it first increases the oxidation potential of cytochrome A. This elevated *oxidative reduction* potential is passed down to the other cytochrome enzymes, whereupon there is an oxidation of nicotinamide adenine dinucleotide dehydrogenase and flavin adenine dinucleotide, reduced form to nicotinamide adenine dinucleotide and flavin adenine dinucleotide in order to provide an oxidizing environment for the substrates of the Kreb's cycle. As a pyruvate is broken down in the mitochondria in an aerobic fashion, there are approximately 15 high-energy phosphate bonds formed. With the formation of two pyruvates from each glucose molecule, 30 high-energy phosphate bonds are formed from the aerobic breakdown of glucose which is 15 times greater than the anaerobic formation of high-energy bonds from glucose in the cytoplasm. The high-energy compound, adenosine triphosphate, is formed from the lower-energy compound, adenosine diphosphate, in the presence of an effi-

*See Test Your Word Score, page 753.

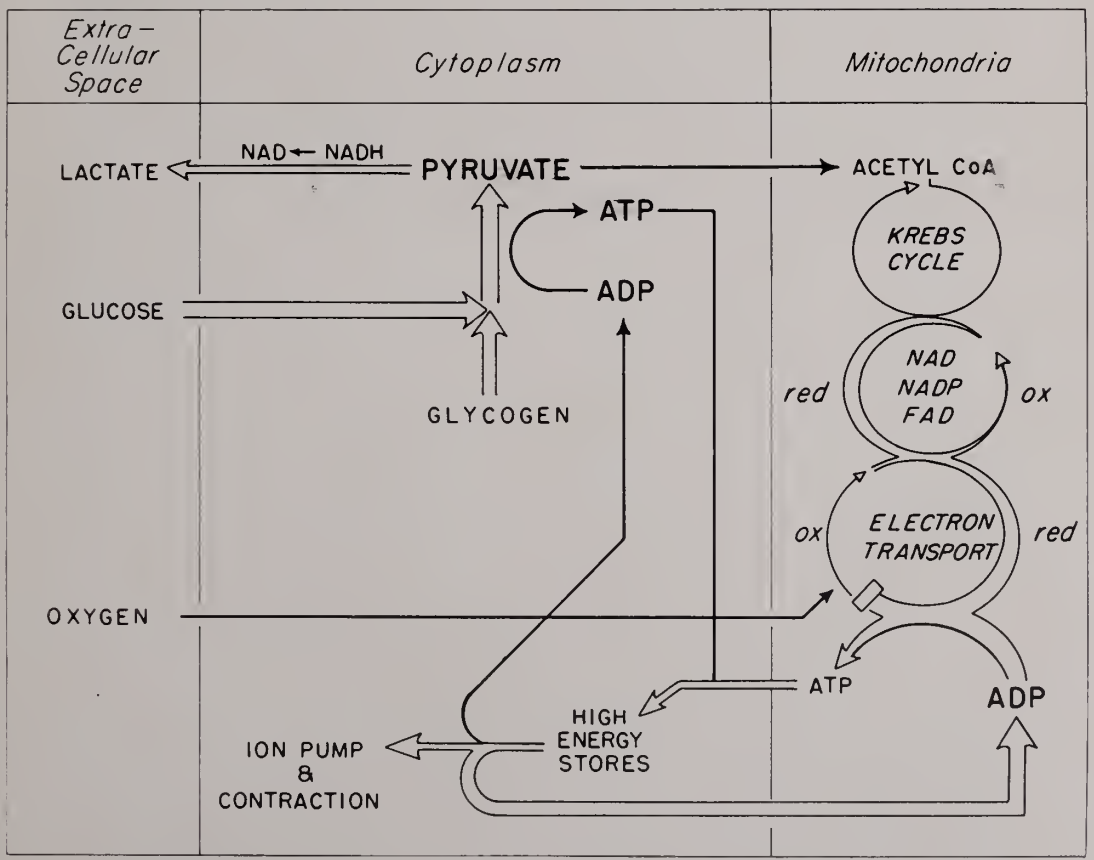


Fig. 4—Outline of anaerobic metabolism of myocardial cell. This figure and Figure 3 were modified from Scheur.[9]

cient oxidative phosphorylation system.

With a shift to anaerobic metabolism of the myocardial cell, one is able to discern changes in the formation of various metabolic products (Figure 4). It would appear that there is less uptake of free fatty acids as well as decreased uptake or perhaps even a production of lactate by the myocardial cell. The uptake of glucose, however, appears to be increased as well as the breakdown of glycogen into the form of glucose. Large amounts of *pyruvate are formed* by the anaerobic glycolytic pathway in the cytoplasm in an attempt to provide the cell with its critically needed adenosine triphosphate. However, since the anaerobic breakdown of glucose is not very efficient in producing high-energy phosphate bonds, it is only for a short period of time that the cell is able to continue its functions of maintaining its contractility as well as preserving the ionic gradients across the cell membranes. *With the decreased oxygen uptake,* there is an accumulation of cytochrome A in the reduced form; therefore, the adenine dinucleotides accumulate in their reduced form and *the Kreb's cycle comes to a halt.* Meanwhile, in the cytoplasm, the oxidative reduction ratio of flavin adenine dinucleotide, reduced form and flavin adenine dinucleotide is such that there is a conversion of pyruvate to lactate and a release of the lactate out into the venous drainage.

Chemical Mediators

The ischemic theory for myocardial pain has previously been based on retrospective observations. The coronary arteries of patients who have died with a history of angina have been found to be narrowed or occluded. Furthermore, the regions which have been served by these vessels are necrotic or scarred. Also, clinical factors which would tend to favor cardiac hypoxia often precipitate or aggravate the anginal syndrome.

Lactate

Cohen et al.[10] have used the concept of excess lactate production to objectively determine the anaerobic metabolism associated with anginal attacks. Although Huckabee's formula[11] for the production of excess lactate has been criticized as not being fully representative of the processes inside the myocardium in relation to the oxidative-reduction potential, nevertheless, it is at present the best indicator that we have for measuring the degree of anoxia associated with anaerobic states. His formula, shown in Figure 5, assumes that the ratio of reduced flavin adenine dinucleotide to oxidized flavin adenine dinucleotide in the mitochondria can be equated to the excess lactate. Strictly speaking, this is probably not true, for the lactate and pyruvate which are being measured come from the blood, whereas the flavin adenine dinucleotide, reduced form, and the flavin adenine dinucleotide which are to be represented are found inside the mitochondria. One cannot assume that the oxidation reduction potential in the mitochondria is the same as that in the cytoplasm; furthermore, one cannot assume that the oxidative reduction potential in the cytoplasm is the same as that of the interstitial space; and finally, the potential in the interstitial space cannot be likened to the composition of the compounds in the blood. Nonetheless, the concept of excess lactate has proven to be quite valuable as a research tool in the evaluation of anaerobic metabolism.

$$\text{Excess Lactate} = (L_o - L_f) - (P_o - P_f)\,\frac{L_o}{P_o}$$

L_o = Arterial Concentration of Lactate

L_f = Venous Concentration of Lactate

P_o = Arterial Concentration of Pyruvate

P_f = Venous Concentration of Pyruvate

Fig. 5—Huckabee's formula for excess lactate.

Cohen has found that in the catheterization of the coronary sinus of normal patients there is an excess lactate found in approximately 11 percent, whereas in *patients with coronary artery disease there is an excess lactate found in 63 percent.* Of those patients who have coronary artery disease and an anginal attack at the time of catheterization, 88 percent demonstrate an excess lactate. Furthermore, Cohen has demonstrated that normal patients extract approximately 30 percent of the lactate in the arterial blood. However, he has also shown that of those patients who have angina at the time of catheterization approximately 50 percent will produce lactate. Most authors feel that lactic acid is not the primary cause of pain

associated with angina pectoris.

Kinins

Kinin is the generic term for a group of polypeptides consisting of approximately nine amino acids with a molecular weight of 1,000; most of which begin and end with arginine.* They are being extensively studied at the present time[12,13] and have been shown to possess potent biological activities consisting of smooth muscle contraction, the ability to induce hypotension and to increase the blood flow to certain viscera, as well as to increase microvascular permeability. From a physiological standpoint it is felt they regulate the flow of blood to the salivary glands and play a role in the constriction of the ductus arteriosus. Pathologically, they are felt to play a role in arthritis, asthma, foreign-body granulomas, endotoxin shock, migraine headaches, and in the inflammation of thermal burns.

Plasma kinins, such as bradykinin, are thought to be derived from a plasma kininogen which has been identified as an alpha globulin. Under the influence of the kallikrein enzyme system, plasma kininogen is broken down into a decapeptide and then into a nonapeptide which is the active form. This activated kinin can then be broken down under the influence of kininase into an inactive kinin by the removal of one of the amino acid groups. Edery and Lewis[14] have done in-vitro work to show that the activity of bradykinin appears to be increased in the presence of an acid medium, which conceivably could exist in the presence of tissue anoxia. Pitt[15] and his colleagues, utilizing coronary sinus catheterization studies, electrocardiogram changes of ischemia, were able to demonstrate that five of seven patients showed an activation of the kallikrein system. They also studied two patients without evidence of ischemia and found no activation of the kallikrein system.

Bradykinin has been further studied by Guzman and his colleagues[16] with an analysis of the pseudoaffective response. This response, consisting of vocalization, hypernea and hypertension, has long been recognized by biologists as a way of determining pain in an anesthetized animal. By this method one is able to determine which compounds in the coronary arteries cause pain. Although potassium chloride, acetylcholine and 5 hydroxytryptamine, as well as histamine, all gave a response, it was evident that the crude *bradykinin and the synthetic bradykinin produced the most recognizable reaction.* Other arteries which were effective in producing pseudoaffective pain responses to the injection of bradykinin are branches of the abdominal aorta, muscle branches, and some of the cranial vessels.

Although the evidence so far indicates that the kinins may be capable of inducing pain, there are theoretical objections to their being chemical mediators of the anginal pain. One objection is that pain is very uncommon in myocarditis and it is known that kinins are released in large quantities in inflammation. Furthermore, a generalized ischemia of the heart may not cause pain, although localized areas of ischemia produced by the ligation of a branch of the coronary vessel may cause pain. Also, similar degrees of chemical ischemia which may produce constant amounts of bradykinin may or may not initiate pain. This third factor, of course, may be related to the alterations of pain stimuli which have been previously discussed.

Nucleosides

Nucleosides appear to be assuming an important role in coronary circulation, for it is believed the coronary flow is controlled by the release of a nucleoside into the interstitium of the myocardium. In order to evaluate these compounds, an analysis of the breakdown of the adenylic acid from the myocardial cell is shown in Figure 6. A nucleotide which consists of a base, a sugar, and a phosphate group under the influence of a phosphorylase enzyme can be broken down into a nucleoside which consists of a base and a sugar.[17] In the case of adenosine, the base is guanine and the sugar is furanose. When adenosine is subjected to a deaminating enzyme, inosine is formed which may be further broken down into hypoxanthine. Adenylic acid in the skeletal muscle has been shown to be deaminated and immediately broken down into inosinic acid.[18] Here adenosine is not formed. If one were to speculate that adenosine could act as a coronary vasodilator as well as a chemical stimulant to the pain fibers, one would have to demonstrate that, at least in the myocardial cell, adenylic

*See Test Your Word Score, page 753.

acid would be broken down to adenosine. It had already been shown that adenosine causes vasodilatation in the coronary bed. Furthermore, adenosine has been known to be rather potent in this respect, and there is a large source for adenosine in the myocardium in the form of adenylic acid. Adenosine has also been shown to penetrate the myocardial membrane and to be rapidly inactivated. As it is inactivated to inosine and hypoanthine, its activity as a vasodilator is lost.[19] Katori[20] has demonstrated that under the influence of hypoxia, inosine and hypoxanthine are found in the venous drainage although not present in the arterial infusion and that they therefore come from the myocardial tissue. No adenosine, however, is found. But when an isolated heart is perfused with a hypoxic solution in the presence of 8-azoguanine, then not only inosine and hypoanthine but also adenosine is found. 8-azoguanine is a known inhibitor of adenosine deaminase and by inactivating this compound adenosine can be found in the perfusate because it is not destroyed. However, the significance of the adenosine is not clear.

Lysosomes

Lysosomes were first postulated by deDuve in 1955, at which time, without the aid of their visualization, he predicted that they consist of a multiplicity of enzymes (acid hydrolases) and that these enzymes would have a spatial-linked latency, i.e., they would be separated from their substrates by some sort of membrane. Novikoff in 1956 demonstrated lysosomes in cells, utilizing an electron microscope and fluorescent dyes. Under the influence of noxious stimuli, the membrane surrounding the lysosome may be broken down or at least made more permeable, so that there may be a release of these lysosomal enzymes into the cell where they may act upon their substrates (Figure 7). At present there has been no experimental evidence that myocardial lysosomal enzymes are responsible for the pain associated with angina pectoris; however, there have been some ischemic myocardial lysosomal studies which have

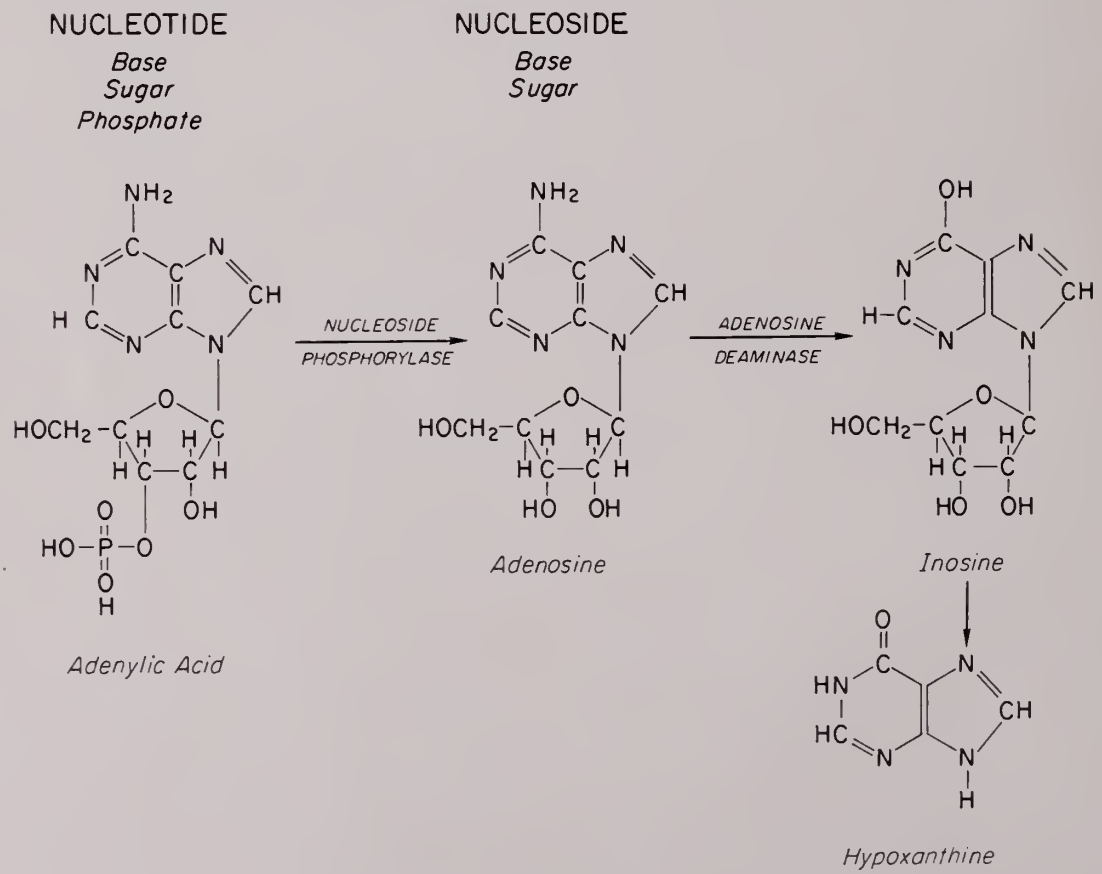


Fig. 6—Breakdown of adenylic acid from myocardial cell.

demonstrated that proteolytic cathepsin which is active at a low pH has been demonstrated in an active form in rat hearts that have been perfused with a solution with a decreased oxygen tension.[21] Other studies have demonstrated a non-homogenous release as well as a selective retention of lysosomal hydrolases in ischemic hearts.[22] It would be pure speculation to say that lysosomal enzymes are important in the genesis of anginal pain; yet it is conceivable that perhaps some of the compounds which they produce through their enzymatic activity may play a role in the genesis of the anginal syndrome.

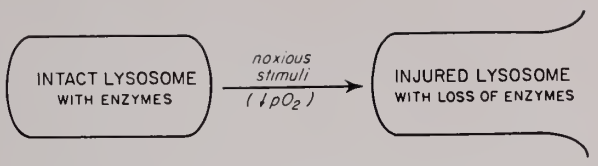


Fig. 7—Concept of loss of lysosomal enzymes with injury to lysosomal membrane.

Summary

At the present time we do not have a biochemical explanation for angina, although much new understanding is accumulating in this area. With increased emphasis on the problem and a greater comprehension of the pathophysiologic processes involved in the production of this common syndrome, newer pharmacologic tools may be developed to alleviate its pain. In addition to the therapeutic gains which can be achieved, perhaps of as much import will be the information obtained in a spin-off fashion which can be applied to other areas of cardiovascular evaluation in determining the efficiency of a given operation to provide adequate tissue oxygenation.

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Doctors

When I was young there were children's doctors but no pediatricians, ear-nose-and-throat surgeons but no otolaryngologists, skin doctors but no dermatologists, mad doctors but no psychiatrists.—Sir Ernest Gowers

Ailments of Men in History

The Lonely Nietzsche and His Migraine

From youth onward Nietzsche was subject to dreadful headaches, often accompanied by vomiting and intense pain in the eyes. He had temporary strokes of paralysis, and sometimes lost the power of speech. Probably the disease from which he suffered was what we now call migraine or "sick headache." This is a trouble that is almost confined to persons of active and intelligent mind, and the cause of it is quite unknown. Nietzsche, imagining that his headaches had something to do with his digestion, used to starve himself and lead the most ascetic life; but all to no purpose. Starvation rather tends to make the patient worse. As a rule this sickness tends to improve as the patient grows older; but in Nietzsche's case advancing age brought no relief. Work was impossible, and he had to get leave of absence from his position as Professor of Classical Philology in the University of Basel in 1876. Later on he tried to resume work, but spent many years in wandering from one health resort to another in almost constant pain; indeed, he said that for him two hundred days out of every year were days of pain.

Late in the year 1888 the blow fell; and Nietzsche became definitely insane. The first symptom seems to have been that his Italian landlady noticed that Professor Nietzsche had suddenly taken to imbibing gigantic draughts of water. Suddenly, while he was walking near his home, he fell down in the street and could not get up again; that is to say, probably one of his cerebral arteries had gone into a state of spasm. His landlord found him and helped him home, where he lay for two days on a sofa in a lethargic, probably semi-conscious, state; he would not say a word nor answer questions. When he awoke to the world again he was deranged.

They took him to Jena, where he was admitted to an asylum. Unhappily his friends had no specimen of his handwriting to assist the asylum doctors, and as it was before the days of the cerebrospinal Wassermann test, it is not surprising that the poor doctors, driven to give the thing a name, hinted at general paralysis, though they seem to have eaten their words later.

Faithful to the principle that no doctor ought to offer a diagnosis without having seen the patient, I hesitate to say definitely what was the matter with Nietzsche; but I should not wonder if the poor overwrought man was suddenly seized by something akin to melancholia, that last infirmity of sensitive minds. As clods do not suffer from migraine they comparatively rarely attain to the heights—or depths—of melancholia. Under the influence of nursing, rest and protection from the attacks of the world, he partly recovered, but, as generally happens with melancholia in middle age, he seems to have become more emotional and partly demented before the chronic trouble that may have caused his headaches ultimately killed him. Throughout his insanity the difficulty in speaking pursued him. "I don't speak prettily," he would pathetically say; and after a tremor that may have been uraemic he passed away.*

*C. MacLaurin: Post Mortems of Mere Mortals, 1925.

Editor's Note: In this modern day the ADH vasopression studies and search for a brain lesion might have been in order.

You can't get rid of a bad temper by losing it.

The Curious Clyster

A Strange Rectal Tumor

D. G. McQUARRIE, M.D.*

THE PERVERSIONS, peculiarities, and therapeutic foibles of self-medication can always be a source of challenging diagnosis. Embarrassment cloaks the cause of the problem with historical vagueness when the rectum and urogenital tract are involved. The following case adds one more weird differential diagnosis to file under "cancer of the rectum—spurious causes."

Case History

A taciturn 71-year-old veteran was admitted to the Minneapolis Veterans Administration Hospital with a two-day history of diffuse, mild, lower abdominal pain. He reported having had a "fever" and one episode of "chills." The admitting physician felt a firm circumferential rectal mass. The patient and his wife denied any symptom suggestive of rectal carcinoma or disease except for a two- to three-month history of constipation.

Past History

Past medical history was complicated by a long series of treatments and operative procedures for urethral stricture culminating in a perineal urethrostomy in 1963. He had had cataracts and a retinal detachment successfully treated in 1965. Twelve months prior to his present admission, he had been admitted and observed for abdominal pain which proved to be due to a severe urinary tract infection. At that time, there was no pathology seen on proctoscopy and barium enema. He was known to be a mild diabetic managed by diet.

Physical and Laboratory Findings

On the day of admission, abdominal films showed air in both the small bowel and the colon down to the sigmoid. One or two air fluid levels were present, suggesting a mild ileus or partial intestinal obstruction. A low-pressure dilute barium enema showed a constricting deforming lesion confined to the upper rectum "suggesting a neoplastic process" (Figure 1). The WBC was 8600 with 71% PMNs. Hgb was 14.5. Urine no WBC's, culture sterile, BUN 23, FBS 118. Other studies were noncontributory.

At proctoscopy, a circumferential firm bluish-black nontender mass was easily visible beginning at 6 cm. The upper extent was not seen. There was no ulceration in the lower visible portion. Several biopsies were taken at this time. The pathologist reported that the biopsies showed "necrotic debris with granulation tissue" (Figure 2). On the sixth hospital day the patient was re-proctoscoped. This second time, the lesion was more indurated and clearly "appeared neoplastic." It was circumferentially irregular, black to blue-grey in color. The biopsies taken this second time showed "acute non-specific colitis" (Figure 3).

Misleading X-Ray Report

A repeat barium enema showed an "annular neoplastic lesion." The remainder of the colon appeared normal. There was no significant obstruction.

On examining the patient several days later on the ward, it was "obvious" to the resident and consulting staff that the previous proctoscopists had simply failed to biopsy the now ulcerated "clear-cut cancer." Since the patient's previous lack of cooperation was thought to be a contributing factor to the unsuccessful biopsies, and since he volunteered a few salty epithets when told of another



Fig. 1—A view of the constricting rectal lesion with the balloon in place. Lesion appears just above the balloon.

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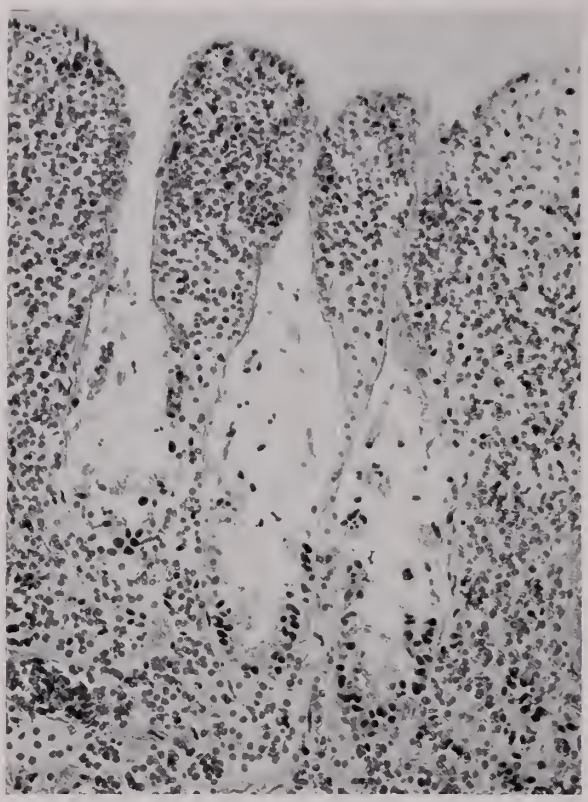


Fig. 2—Necrotic rectal mucosa from first biopsy. Note the infiltration of red blood cells.

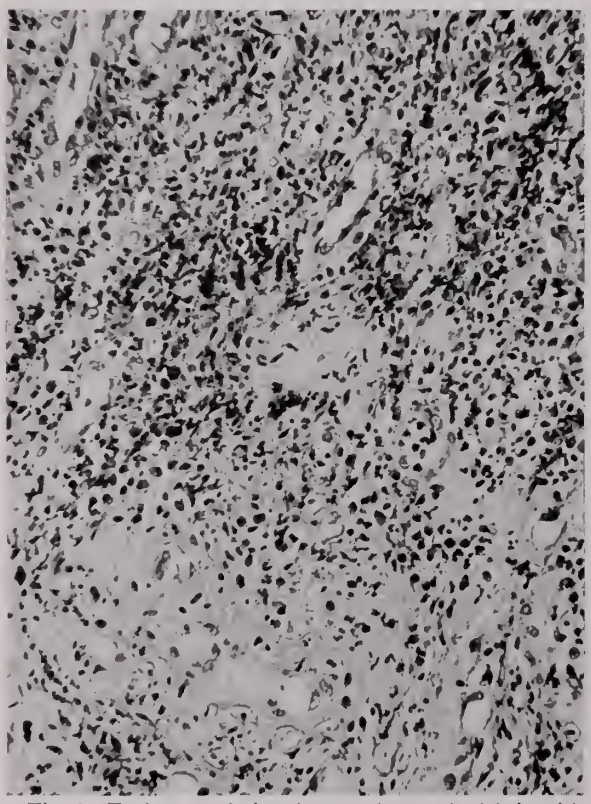


Fig. 3—Early granulation tissue and necrotic debris with leukocytic infiltrate.

biopsy, a caudal anesthetic was administered for proctoscopy. On the third examination, 18 days after admission, the lesion was an ulcerating circumferential lesion with a heaped-up multilobulated, exophytic, irregular border. Multiple frozen sections were all returned as showing acute inflammatory reaction with granulation tissue (Figure 4). Mucosa was seen to be undermined with an inflammatory process. Ganglion cells were visible on one section confirming adequate depth of biopsy.

Retrospectroscopy

Turpentine Enema

Armed with a better assurance of an acute inflammatory lesion, possibly secondary to some caustic or thermal injury, the patient was again questioned about causes of rectal injury or unusual enemata. With some relief that the physicians had found the cause of his problem, the patient admitted that two days prior to admission, his wife had made an enema of lux soap and water with a dollop of turpentine. This enema solution had been heated to a boil on the stove and placed in an enema bag. Without pause, the quart or so of dilute, hot, Procter and Gamble product was promptly instilled into the patient's rectum. In the patient's own words but without his dramatic emphasis, "It was like as not to burn out my whole insides." His wife confirmed the episode. It appeared that embarrassment had prevented either of them from mentioning the episode.

Treatment

Over the next two months, the patient was given a low-residue diet, metamucil as a stool softener, and cort-enemas. These cort-enemas were administered daily over the first month and at progressively extended intervals thereafter. The rectal lesion was observed weekly. Healing took place gradually. At about two months post burn, some stricture was developing; so the stenotic area was dilated to 15 mm. on two occasions. After this, the proctoscope could always be passed to 25 cm. without difficulty. On last follow-up, the patient was doing well and was without stricture. The lesion was healed.

Discussion

This case is illustrative of a number of points, not the least of which is that otherwise sensible patients will occasionally use clearly

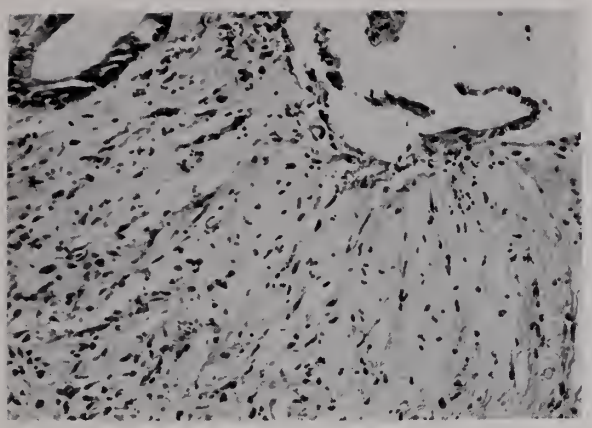


Fig. 4—Biopsy from edge of lesion showing loss of mucosa and underlying inflammatory tissue.

harmful self-medication with no discretion. After the harm is done, they will go to great lengths to conceal their blunder.

In the folk medicine of our older patients, the enema is still regarded as the panacea of many ills. As Dr. B. F. Weaver[1] observed, "Flushing the bowels with warm water . . . affords immediate relief in stomach and bowel troubles, and if kept up, purifies the entire system. It is a specific for kidney, liver, and lung trouble, cleanses and beautifies the skin. . . . It affords relief and cure to almost all female disorders." These attitudes published in a 1903 proprietary "Doctor Book" reflected the practice of the preceding three centuries. Even Lorenz Heister's classic description of appendicitis in 1755 proposed treating this inflammation with "clysters prepared with emollient and discutient* herbs . . . used frequently . . . as they reach the part and resolve the inflammation."[2]

The enema has been slow to fade in importance in popular use against centuries of unquestioning devotion to its traditional employment in all diffuse disorders. It is not surprising that older patients seek medical advice only when an enema fails.

Rectal Burn

The second point of the case is that it gives an unusual opportunity to observe the clinical course of a full thickness scald of the rectum. Two days after such an injury, there is a firm hard edema of surrounding tissues. The mucosa is darkly colored, presumably reflecting the capillary thrombosis in the burned mucosa. The mucosa sloughs over the next seven to 12 days, leaving a hypertophic granular base. Edema and proliferating granulation tissue grossly mimicking carcinoma may persist for a month or so. In managing this case, there were (in retrospect) no signs forcing a diverting colostomy, although circumstances could have made one necessary. Diversion of the fecal stream was not done in hopes of avoiding an uncorrectable stricture. Healing occurred over three months despite the burn being circumferential and 4-5 cm. long.

The final point is self evident: The folly of mankind is always open to new invention.

*See Test Your Word Score, page 753.

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Expense Accounts

Many minor executives prefer a generous expense account to a raise in salary, which would be more heavily taxed and more soberly spent. It is they who support the so-called expense account restaurants, places of exotic decor where patrons lunch in a darkness which is all but complete. They cannot see to read the prices on the menu, but these, in the special circumstances, are irrelevant.*

*C. Northcote Parkinson

Making Time

The wicked flee when no man pursueth, but they make better time when someone is after them.—Charles Parkhurst

Historic Hospitals

The Order of The Holy Spirit



Heilige Geist Hospital, Schwäbisch-Gmünd. Courtesy National Library of Medicine, Bethesda, Maryland.

Prior to the thirteenth century, hospitals in the western world were remote institutions serving as hostels for travelers or as asylums for the needy and infirm. As charities operated by the Church, they possessed little of a medical character.

During the Crusades, several religious orders were formed in the Holy Land about hospitals which had been previously organized by Italian and German merchants. These hospital orders provided domiciliary and nursing care for the sick and injured European combatants in the long, drawn out campaigns of the holy wars. The idea of hospital orders returned with the Crusaders to Europe where more such orders were formed, the most important being the Order of the Holy Spirit.

At the same time, Europe was undergoing sweeping changes. The feudal system was dying, the economy changing from agricultural to mercantile and the growth and development of cities flourishing. The concentration of population in the cities brought a need for more hospitals. Accordingly, the Order of the Holy Spirit, in the greatest hospital movement of the Middle Ages, built more than 1250 hospitals, mostly in European cities.

Interestingly, the first modern man to appreciate the important role of the hospital orders in history was Rudolf Virchow, the great German pathologist, anthropologist and political activist. Virchow was interested in the history of hospitals, and in 1877 he wrote a monograph on the Order of the Holy Spirit in which he pointed out that its hospitals were built in population centers and that they possessed some characteristics of medical institutions. Many of these hospitals eventually came under the control of secular city administrations, and Virchow believed them to be the points of departure in the development of modern medicine.

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Liver Disease and Phenothiazines

Involuntary Movements

MILTON ETTINGER, M.D.* and JOHN CURRAN, M.D.†

Side-effects of medications often prove to be of as great importance as their therapeutic effects, and this certainly has been true of the phenothiazines. Their introduction was followed by descriptions of a multiplicity of side-effects, including several related to the motor system. Parkinsonian-like movements, dystonic movements, and akathisia‡ are well accepted now as involuntary motor movements caused by phenothiazines, disappearing when these drugs are discontinued.

Less well accepted as a disorder of movements related to phenothiazine administration is the so-called tardive dyskinesia syndrome or "perioral" dyskinesia. The current status of this alleged side-effect is reviewed in recent reports by Crane[1] and Kline.[2] While these authors disagree on a number of variables—incidence, etiology, description, reversibility—they share one significant omission: neither of them considers at length the role of the liver in the genesis of these movements.

The purpose of this communication is to present evidence which suggests that some observers may be confusing a not uncommon but relatively unknown degenerative hepatocerebral condition with drug side-effects.

Background

Patient Source

In 1965 Schiele and Curran conducted a survey at the Fergus Falls State Hospital (Minnesota) to determine the incidence of the tardive dyskinesia syndrome, since a literature review from several countries suggested that this would be an instructive exercise.[3] This was accomplished by furnishing the hospital staff with a composite description of the syndrome culled from the literature and asking them to nominate likely candidates. Thirty names were submitted from the more than 1000 patients then hospitalized. Upon examination, 15 of these were dismissed from further consideration when some other explanation than a possible drug reaction seemed plausible (one case —Parkinsonism, 11 cases—mannerisms and tics associated with chronic schizophrenia, three cases—poorly fitting dentures). In two other patients no involuntary movements were present.

Evaluation

The remaining 13 patients were then observed and each involuntary movement attributed to the syndrome was rated on a four-point scale. Any involuntary movement peculiar to the patient but not described in the literature was also recorded and rated. One rater performed all the ratings. Charts were then searched to determine if any common variable was present. In five cases records were too incomplete or fragmentary to be included in the review. In the other eight cases the record review did not establish any reasonably certain relationship to the ingestion of medications, although most had received considerable doses of phenothiazine medications.

Early Conclusions

It was concluded that (1) involuntary perioral movements were not uncommon in a state hospital population; (2) it was impossible to clearly determine the relationship of such movements to drug load; (3) it was impracticable to pursue the matter further because of lack of clarity in the definition of the syndrome.

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Possible Relationship to Hepatic Dysfunction

Matters rested there for three years until our attention was drawn to an article by Victor et al.: "The Acquired (Non-Wilsonian) Type of Chronic Hepatocerebral Degeneration."[4] This paper presented 27 cases of hepatocerebral degeneration thought to be long-term sequelae of non-hereditary hepatic dysfunction. Some of these cases were followed for more than 15 years. A progressive downhill course was a constant feature. The results of post-mortem examinations were available in 17 cases and could be reliably distinguished from hereditary hepatocerebral degeneration, i.e., Wilson's disease. However, the authors concluded that distinction between the acquired and non-acquired forms on clinical examination alone was difficult, and that a definitive diagnosis required studies of copper metabolism, slit-lamp ophthalmoscopy, and a careful review of the family history.

Movement Disorders

Of particular interest to us, however, was that one prominent clinical feature of the syndrome was movement disorders of several varieties. As a matter of fact it appeared that the syndrome of neurological abnormalities described by Victor et al. seemed quite similar to the various descriptions of the tardive dyskinesia syndrome. A point-by-point comparison of the two follows:

Acquired Hepatocerebral Degeneration

1. A wide range of neurological abnormalities is present. No case is considered typical but most patients have a majority of the findings described.
2. Impairment of intellectual functioning is common.
3. Dysarthria is present in most cases, so severe in eight that the patients could not communicate.
4. Cerebellar disease (ataxic gait, intention tremor) is present in 24 of the 25 cases.
5. Involuntary movements of extreme variability in severity and extent are present in 16 of 25, usually affecting the limbs. In four cases, however, the tongue and face are the most affected portion of the body.
6. The course is variably progressive, with no recovery.
7. Hepatic dysfunction is thought to be part of the etiological chain.

Tardive Dyskinesia

1. Such a wide range of movement abnormalities has been described that a precise definition of the syndrome is difficult. (This problem of establishing criteria is what stymied any elaboration of the survey described above.)
2. Brain damage with impaired intellectual capabilities has been consistently described and usually attributed to multiple courses of electroconvulsive therapy (ECT), to lobotomy, to defective cerebral circulation or to drugs.
3. Dysarthria is not emphasized in most publications but was noted in Hunter's case description,[5] also Evans'.[6]
4. See the case reports of Druckman,[7] also Hunter.[5]
5. Involuntary movements are one of the cardinal features of the syndrome.
6. Irreversibility is one of the hallmarks of the syndrome, according to some.
7. Hepatic functioning is usually not mentioned, although one of Evans'[6] cases did eventually develop hepatic decompensation. One of Druckman's cases[7] is reported to have ingested one pint of alcohol daily for more than 10 years. Schmidt et al.[8] describe a case with cirrhosis and coma. Most observers, however, do not present any evi-

TABLE I
Follow-up Condition of Eight Subjects

Subject	Clinical Condition	Laboratory Tests: BSP 5 min.	BSP 30 min.	Other
1.	Fewer involuntary movements	Not done		Not done
2.	Fewer involuntary movements	72	6	Within normal limits
3.	Fewer involuntary movements	Not done		Within normal limits
4.	No involuntary movements	110 105	28 33	Within normal limits
5.	No involuntary movements	96 66	14 10	Within normal limits
6.	Fewer involuntary movements (Chart, however, suggests no sustained improvement)	92 92	23 37	Within normal limits
7.	Worse	64	8	Within normal limits
8.	Much worse	Not done		Alb.=3.1; Glob.=4.5 Ceph. floc. negative

dence in their case reports by which hepatic functioning can be evaluated. Perhaps the only case report in which hepatocerebral degeneration of either variety is clearly ruled out by extensive documentation of normal hepatic functioning and normal copper metabolism is that of Ekbom.[9]

Possible Misinterpretation

We concluded that published case reports of acquired hepatocerebral degeneration are quite similar to some case reports of the perioral dyskinesia syndrome. It was logical to suppose, therefore, that psychiatrists were misinterpreting or misdiagnosing a neurological entity which was not only uncommon, but also not widely appreciated even among neurologists. If so, this could explain at least one of the more puzzling issues surrounding the tardive dyskinesia syndrome, i.e., the issue of irreversibility. A random sprinkling of acquired hepatocerebral degeneration among the various series would explain why some cases appeared to remit while others progressed in an alarming fashion to serious disability.

Follow-Up

The opportunity to examine this hypothesis was conveniently at hand. If it was true, a follow-up of the 13 patients identified three years earlier as possible cases of the tardive dyskinesia syndrome should reveal some evidence of hepatic dysfunction within the group.

The actual follow-up procedure involved interviewing the survivors, rating their behavior in the same manner as before by the same rater, reviewing their charts, and obtaining tests of liver function. Such tests included bromsulphalein retention (BSP), total serum protein with albumin/globulin ratio, cephalin flocculation, and serum glutamic oxaloacetic transaminase (SGOT), although it was not possible to perform each test in every case.

Results

Two patients had died; in one case the cause of death was unknown since it had occurred following discharge. Autopsy findings were available on the other patient and indicated the presence of centrolobular fatty metamorphosis and centrolobular necrosis of the liver, both acute, and presumably caused by terminal heart failure. A review of the hospital charts of both revealed no history or clinical findings sugges-

TABLE 2
Clinical Ratings of Three Subjects

	Case 6		Case 7		Case 8	
	1966	1969	1966	1969	1966	1969
HEAD	2+	0	0	0	0	0
Rolling of tongue inside lips	1+	0	0	0	2+	3+
Munching and chewing	0	0	2+	2+	0	0
Mouthing words	0	0	0	0	0	0
Slurred speech	2+	0	0	0	2+	0
Lip pursing or puckering ("fish-mouth")	2+	0	0	0	0	0
Protrusion of tongue ("fly-catcher")	0	0	0	3+	0	0
Rocking						
LEGS	2+	1+	0	0	0	0
Tapping or paddling	2+	0	2+	0	3+	3+
Restlessness	0	0	0	0	3+	0
Crossing and re-crossing	0	0	2+	0	0	0
Tremor	0	0	0	2+	0	0
Swinging when crossed	0	0	0	0	0	2+
Extension at knee						
ARMS	2+	0	0	1+	0	0
Restlessness	0	0	0	0	2+	0
Caressing hair or face	0	0	1+	2+	0	0
Writhing hands						
TRUNK	0	1+	0	2+	0	0
Rocking	2+	0	0	0	0	3+
Restlessness						
GAIT	0	0	2+	3+	0	(Unable
Postures and struts						to walk)

0 = not present 1+ = barely present 2+ = definitely present but unobtrusive 3+ = socially disabling

tive of chronic hepatic disease.

Of the 11 surviving patients, only eight could be interviewed. A review of their charts revealed no evidence of hepatic dysfunction.

Table 1 summarizes the results of the clinical ratings and the hepatic function testing.

It will be seen that five of the eight patients manifested either fewer involuntary movements or none compared with three years previously. Two were definitely worse. One patient, Case 6, was rated as having fewer involuntary movements; yet his course indicated that a considerable movement disorder was present which fluctuated in intensity. This was not seen in the review of the records of the other cases.

Table 2 contains both ratings for the three subjects who were unimproved or worse on follow-up. Their case reports follow:

Case Reports

Case 6

When this 62-year-old white male was first interviewed he had been hospitalized for 22 years. During this interval he had received 27 electroconvulsive therapy treatments as well as the equivalent of 150 mg/day of chlorpromazine for four years. On the occasion of the initial testing, in addition to the involuntary motions noted in Table 2, increased resistance to passive motion of the wrist was present.

In December 1967, 22 months after his first rating, a review of his career contained the following comment: ". . . on tranquilizing drugs . . . develops parkinsonian features with facial mannerisms, jerks of his shoulders and a kind of stiff walking." Later he was described as "pacing" with respiratory irregularities. In January 1968, "continuous compulsive groaning with a crescendo rhythm" was noted. "Grimacing" and "groaning" were partially controlled with amytal. Haloperidol, 5 mg/day, was started in May with a subsequent decrease in moaning, jaw movements, and rocking movements. Athetoid movements and coarse tremors of hands and feet were noted in August 1968. In April 1969 "another spell of compulsive grimacing . . . groaning like exercising his jaw . . . rocks himself while sitting." It was also noted that when he was alone the unusual movements were not present.

At the time of the follow-up rating, his posture was somewhat rigid, cogwheeling was present during passive motion of the left arm, and occasional fine rhythmic tremors appeared in the left arm and right leg. Practically no other involuntary motions were observed. He was thought to be unimproved.

Comment

Features suggestive of Parkinsonism were a consistent finding in this case, the etiology of which is not clear. The chart notations clearly indicate, however, that other motor abnormalities were present as well, although these appeared to fluctuate in intensity more than the Parkinsonism did. On one occasion haloperidol was thought to be effective in reducing the involuntary movements, while on other occasions reducing the stimulus input was seen as an ameliorative factor. No observations were present describing variables increasing the involuntary movements. It should be noted (Table 1) that there is a marked abnormality in bromsulphalein retention.

Case 7

This 52-year-old lady had been hospitalized for 25 years when first rated. She had received a lobotomy, 301 electroconvulsive therapy treatments, as well as the equivalent of 400 mg/day of chlorpromazine for 11 years. In June 1960 the venereal disease research laboratory test was noted to be weakly positive while the Kolmer was doubtfully positive. Apparently these findings were not explored further. The bromsulphalein retention in December 1963 was 14% and 8% at five and 30 minutes respectively. At the time of her initial rating the charts recorded her as hyperactive. A mental status examination revealed that she was disoriented as to place.

In June 1967 an "odd walk" was noted. Shortly afterwards a total abdominal hysterectomy was performed because of vaginal bleeding. The condition of the liver at laparotomy is not known. The annual physical in November 1967 revealed no positive abdominal findings. In January 1968, "she talked as if she were drunk . . . slurred speech." Three months later the neurological consultant reported: ". . . a coarse tremor of lips and perioral region and occasionally seen in hands bilaterally at rest with extension of the arms to a forward position . . . aggravated to a mild degree with finger-to-nose maneuvers . . . difficult tandem walking . . . gait is best described as ataxic. . . ." The diagnostic impression was frontal lobe ataxia, most likely secondary to lobotomy. In November 1968 "extra" motions similar to "athetoid" movements were ascribed to the patient but not described in detail. During the three-year interval between ratings she remained on a moderate-to-heavy drug load consisting of various combinations of thioridazine (500-800mg/day), fluphenazine (2.5 mg/day), and haloperidol (3mg/day). Low normal leukocyte counts and a mild anemia (8-10Gm.Hgb.) were frequently noted.

On repeat examination there was an explosiveness to her speech and movement. She bolted from the chair when called. Constant motion was present. Her gait was broad-based with a lordotic spine, abdomen thrust forward, and exaggerated swings of her arms. No Romberg sign was present and normal rebound responses were seen.

Comment

The impressive neurological signs manifested by this lady can be accounted for in several ways besides ascribing them to toxic drug

effects. Certainly the equivocal serological findings should be investigated. In contrast to Case 6 it appears that here the course is slowly progressive. It is also worthy of note that the records do not in any manner relate drug ingestion to involuntary movements; in contrast to Case 6, haloperidol appears to have no effect on them for better or for worse. Finally, in 1963 and at follow-up (Table 1) bromsulphalein values are unremarkable at 30 minutes (although the five-minute figures are low), while in 1967 an abdominal exploration was performed without cirrhosis being reported.

Case 8

This 74-year-old white female had been hospitalized for five years when first seen. She had received an unknown amount of electroshock therapy during her hospitalization, as well as the equivalent of 150mg/day of chlorpromazine for one year.

When the patient was first seen, a considerable number of involuntary movements were noted (Table 2). The nurses described her as quite disoriented and as "moaning and groaning" constantly. Her gait was normal.

She was maintained on thoridazine 100mg/day and in June 1968 was discharged to a nursing home. The nursing staff and attending physician there became aware that she was not doing well and welcomed our follow-up inquiries. She was described by the nurses as "always on the go," and as experiencing transient episodes of facial edema or bloating. A review of her chart indicated she had gained 25 pounds since discharge from Fergus Falls.

On examination a number of involuntary movements were again noted; she was unable to sit or stand still. When asked to walk she would stand in place with constant stepping movements of her feet while her torso twisted to the left. When asked to stand alone, she continued the stepping movements, then began to circle to the right. She moaned constantly and was unable to speak. Increased resistance to passive movement was present in the left arm.

A month later she was described as "better," although her attending physician could not specify exactly how she had improved. She had been placed on phenobarbital and diphenhydramine in addition to her thoridazine. She remained totally disoriented.

Comment

This lady was much worse compared to her first examination. In fact, she was practically helpless because of her gait disturbance and difficulty in sustaining a posture. More involuntary movements would have been recorded on her follow-up examination except for the fact that she had become somewhat rigid. The transient facial bloating, weight gain, and abnormal liver-function testing suggest that when she is "worse" she actually is experiencing subclinical episodes of hepatic coma.

Discussion

Evidence of Hepatic Disease

The bromsulphalein test is usually considered the most sensitive test of liver function. Popper[10] states that 10% retention or less at 30 minutes is normal. Cases 4 and 6 miss this by far and must therefore be considered cases of presumptive liver disease. Case 5 is borderline. The evidence for hepatic disease is strong in Case 8 in view of the marked abnormality of serum protein. In sum, three of the eight patients examined probably have liver disease. If one includes Case 5 (borderline bromsulphalein values) as positive and excludes Case 1 (no liver function tests obtainable), this raises the percentage of positive findings from 37% (three of 8) to 57% (four of 7).

Possible Causes of Hepatic Disease

The etiology of the presumed hepatic disease is not clear. All histories were negative for alcoholism. While it is possible to believe that perhaps in one or two cases families concealed such histories, it would be difficult to assume that such was true of all four positives. Wilson's disease also remains an unlikely candidate until ruled out by the usual studies. Another possibility is raised by Kety who comments on the high incidence of hepatic disease in state hospital populations because of indifferent standards of cleanliness, e.g., viral or amoebic hepatitis or both.[11] The point here is that individuals with a history of prolonged exposure to a state hospital environment are at increased risk of developing hepatic disease and its complications, one of which is hepatocerebral degeneration. Most reports of the tardive dyskinesia syndrome draw from populations largely, if not totally, composed of state hospital patients.

Hepatotoxic Effect of Phenothiazines

A fourth etiological possibility is a subclinical hepatotoxic effect of the phenothiazines which progresses to cirrhosis and hepatocerebral degeneration. This alternative preserves the alleged causality, albeit indirect, of the phenothiazines in the genesis of the tardive dyskinesia

syndrome. There is some evidence of progressive liver disease due to the phenothiazines;[12] however, in such cases the liver disease is usually florid and therefore unlikely to go unreported or unnoticed.

Reversibility of Involuntary Movements

Clinically, six of the eight patients who were re-examined manifested either fewer or no involuntary motions compared with three years earlier. This figure reduces to five if one excludes Case 6 where the chart review suggests that our re-rating did not sample enough behavior. If these five patients ever did have the tardive dyskinesia syndrome, it disappeared in time. It would appear then that this syndrome is hardly irreversible, a point already made by Kline.

A careful inspection of Table 1 reveals that there is no correlation between clinical and laboratory findings. Cases 4, 5 and 6 deserve careful follow-up to determine whether they will eventually qualify for a neurological diagnosis, especially Case 6. Case 7 appears to exhibit definite neurological disease in the face of normal hepatic functioning; hence, hepatocerebral degeneration is probably ruled out. As is apparent from the case report, however, several other possible causes of progressive neurologic disease may be present. Case 8 unquestionably represents hepatocerebral degeneration, type unspecified. Further studies of this subject are planned to rule in or out Wilson's disease.

Conclusion

It would appear that our hypothesis has been amply confirmed. Unsuspected cases of hepatocerebral degeneration undoubtedly have been mistaken for the tardive dyskinesia syndrome. Certainly no case of the latter can be considered adequately evaluated without tests of hepatic functioning. Hopefully some of the controversy surrounding the tardive dyskinesia syndrome will be reduced if attention is paid to this variable.

Similarities between reports of the tardive dyskinesia syndrome and reports of acquired hepatocerebral degeneration lead to the hypothesis that cases of the latter have been unwittingly mistaken by psychiatrists for drug side-effects. To test this hypothesis thirteen patients who, three years previously had been suspected of the tardive dyskinesia syndrome, were re-evaluated. Of the 11 survivors, eight were located. Three, possibly four, had laboratory findings suggestive of hepatic disease; one in fact was diagnosed as having hepatocerebral degeneration.

It is concluded that future investigators of the tardive dyskinesia syndrome should consider the variable of hepatic functioning in planning their research strategy.

Generic and Trade Names of Drugs

Chlorpromazine	Thorazine
Haloperidol	Haldol
Thoridazine	Mellaril
Fluphenazine	Permitil, Prolixin
Diphenhydramine	Benadryl

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If you have knowledge let others light their candles by it.—Thomas Fuller

Urinary Tract Infection in Pregnancy*

COLIN MARKLAND, M.D.†

It has been known for many years that urinary tract infection is a common hazard of pregnancy.[1] The importance and seriousness of this problem was emphasized when Kass showed that 40 per cent of pregnant patients with asymptomatic bacteriuria developed pyelonephritis during pregnancy;[2] several studies have indicated that the prevalence of asymptomatic bacteriuria may be as high as 10 per cent.[3] A reasonable inference from these figures might be that pyelonephritis is a hazard to as many as 4 per cent or more of all pregnancies.

Predisposing Factors

In an excellent review of this whole topic Sims[4] mentions several factors that predispose the pregnant patient to pyelonephritis.

Dilatation of Conducting Mechanism

The well known physiological dilatation of the conducting mechanisms of the urinary tract probably slows down and interferes with urodynamics. This may be combined with glycosuria, endocrine changes, and electrolyte disturbances such as a lowered serum potassium. Similarly, there are changed urinary habits during the later months of pregnancy probably directly related to the increasing size and position of the fetus. Exactly how all of these factors predispose the urinary tract to infection is difficult to say; however, current understanding of urinary tract infection suggests that such factors mentioned may alter the bacterial flora of the lower urethra and that this change in the urethra may initiate cystitis.[5] With acute bladder inflammation, trigonitis may cause ureteral reflux, a common initiating factor in the development of upper tract infection in the form of pyelonephritis.[6]

Urinary Tract Infection

From the recent interest in this subject have come several studies suggesting that urinary tract infection may also be related to a higher incidence of premature delivery and perinatal mortality.[7] It was then suggested that these risks might be diminished if asymptomatic bacteriuria could be promptly recognized and treated with antibacterial drugs, given for either a short course or throughout the pregnancy. However, there has been some disagreement over these findings, and other workers have presented different opinions.[8]

Detection of Urinary Infection in Pregnancy

The detection of urinary infection in pregnancy calls for regular and repeated urinalyses of freshly-voided urine specimens. Besides searching for pyuria, possible bacteriuria can be noted, and the urine cultured. A urine culture is a practical procedure even in the doctor's own office.

Culture Plate

A small amount of the freshly-voided urine can be plated out with a precalibrated platinum loop onto a disposable Agar-Methylene-Blue culture plate and incubated overnight in an inexpensive office incubator; a colony count the following day will give a fairly accurate estimate of the number of bacteria per ml. The common forms of urinary tract infectants, such as the Coliform, Streptococci, Staphylococci, and Proteus organisms can also be easily recognized.

The Stat Test

Another screening test for infection easily

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done by the patient is the Stat-Test (Mallinckrodt) dip-stick test.[10] The first morning specimen of the urine is examined. A significant number of bacteria present in an overnight urine specimen turns the dip-stick pink. In this way, the patient herself, at home, can do a weekly examination for the presence or absence fection at other times.

Treatment

When a urine culture shows a significant urinary tract infection, treatment during pregnancy should not significantly differ from infection during non-pregnancy.

Antibiotics

If the urinary tract infection is symptomatic and accompanied by fever, backaches and chills, an immediate clinical diagnosis of pyelonephritis can be made and treated with the appropriate antibacterial agent. There is no reliable data to define the length of time for which treatment should be given, but experience indicates that treatment with antibacterial drugs for several weeks is probably necessary, after an initial seven to ten days' therapy with an appropriate antibiotic.

During pregnancy, care should be taken to avoid the tetracycline antibacterial agents which might have a potential harmful effect on the developing fetus. There have been some reports[11] that even simple agents such as the sulfa drugs may cause problems when given for months, particularly in the last weeks of the pregnancy.

Management of Urinary Tract Dysfunction

When the diagnosis of pyelonephritis has been made and confirmed by urine culture, and when treatment is started, one hopes for rapid clinical improvement. However, if the clinical picture does not improve within 24 to 48 hours, urinary tract dysfunction must be immediately suspected and appropriate investigations considered to rule out some form of urinary tract obstruction.

Initial investigations would include a check of the residual urine to rule out lower tract obstruction, after which consideration should be given to upper tract problems. In a potentially dangerous situation such as this, where both the mother and the fetus may be harmed by continued infection, limited radiographic studies are more than justified. Obviously these tests should not be done indiscriminately; but if the clinical picture is one of continued infection, much more is to be gained than lost by a thorough investigation. This will include a plain radiograph or an intravenous urogram, the latter with one of the newer and stronger iodine-containing agents which afford excellent visualization of the urinary tract without the need for excessive dehydration of the patient. These studies give further information particularly about renal function and the possibility of obstruction by an opaque calcium stone or a non-opaque type of uric acid stone. Extrinsic and intrinsic ureteral disease may also be demonstrated. A voiding cystourethrogram will rule out other problems of lower urinary tract obstruction and ureteral reflux.

Progress

A period of urethral catheter drainage may allow the detrusor muscle to recover from decompensation due to acute retention.

Associated Ureteral Stones

Small ureteral stones will often pass spontaneously, particularly in the presence of the physiological dilation of pregnancy. An impacted stone can often be dislodged by placing the patient in a slight Trendelenburg position which may allow the acute phase to be brought under control with dehydration and antibiotics. A small stone may frequently then cause no further trouble or may later pass spontaneously. Unremitting obstruction may call for the temporary use of ureteral catheters to establish good urinary drainage. Complete blockage of the ureter with non-function of the kidney, due to a stone or some extrinsic process, may demand surgery notwithstanding the state of pregnancy. Modern anesthesia has facilitated such surgery, so that diversionary nephrostomy or removal of the obstructing agent can usually be accomplished quickly, with an acceptable chance of fetal or maternal complications.

With the problem of asymptomatic urinary tract infection, or of lower tract infection such as cystitis, treatment is essentially the same as previously mentioned. There seems to be reasonable evidence that a fairly short course of chemotherapy can eradicate bacteriuria in the majority of cases. This avoids any potentially adverse effects of prolonged treatment on the

fetus or the mother and, if done in conjunction with careful followup study, should allow over 75% of patients to be controlled for the remainder of their pregnancy.[9]

Urological Evaluation

The Voiding Cystogram

It is not generally realized that the most valuable urological screening test, apart from urinalysis and urine culture, is the voiding cystourethrogram. In this simple test a non-irritating contrast agent, such as sodium acetrizoate, 30% (Cystokon, Mallinckrodt), is introduced into the bladder and held until the patient wishes to void. A radiograph of the pelvis is then taken in the oblique position at the height of voiding. This study shows the function of the urethra, bladder, and ureteral reflux, if present. In a recent series of children investigated for urinary tract infection,[12] the voiding cystogram was uniformly successful in detecting the problem, whereas the intravenous pyelogram indicated abnormalities in only 40% of the patients. Voiding cystourethrography can be performed at any hospital or well-equipped clinic, leaving the *cine intensifier* method for problematical cases. particularly in the postnatal period.

Endoscopy

Further evaluation may include endoscopy when examination of a bladder with a panendoscope and cystoscope can easily be undertaken using a topical local anesthetic. This examination is usually preceded by calibration of the urethra with Olivary bougie sounds, now being used more and more to prove or disprove the presence of urethral disease. External meatal stenosis or some form of internal urethral ring can be demonstrated when the Olivary sound is held up along the course of the urethra. Gripping of the sound at the internal meatus may suggest bladder neck stenosis.

Other Urological Treatment

Correctable Urethral Disease

Recently attention has been focused on urethral disease as the most common cause of lower urinary tract infection. Treatment based on urethral dilatation, internal urethrotomy, and various vesical plastic procedures seems to indicate that many previously unrecognized problems can now be treated successfully: normal function and a sterile urine quickly obtained.[12] If a pregnant patient with urinary infection does not respond to a short course of medication, further search for correctable abnormalities is warranted. Other rare and unusual forms of urinary tract infection may be due to fungal and trichomonal infections. Severe vaginitis may influence and change urethral flora to a significant extent and be a source for an unusual urinary tract infectant.

Ileac Diversion

Ileac urinary diversion is becoming an increasingly common and acceptable way to solve many problems of urinary tract disease.[13] This operation is now increasingly used among younger patients with neurovesical dysfunction. Because it provides a satisfactory drainage system with a sterile urine, it is widely acceptable for a variety of urological problems in many patients who may wish to become pregnant.

There have been recent reports of successful pregnancies with this type of urinary diversion, for a well constructed ileac conduit is subject to no more pressure than a normal ureter. There are probably no objections to pregnancy with this type of urinary diversion, assuming that the kidneys maintain good excretory function.

Homotransplantation

Renal homotransplantation is another consideration found now in young patients who may wish to undertake pregnancy. Harrison[14] has reported successful pregnancies following isologous transplantation between identical twins. Pregnancy following allogeneic transplantation has recently been described, despite potential genetic disturbances due to immunosuppressive drugs.

Conclusions

Evidence continues to show that symptomatic and asymptomatic bacteriuria of pregnancy is a serious condition that requires prompt detection and eradication. The association of urinary tract infection to fetal and maternal morbidity and mortality remains problematical, though recent studies indicate that underlying renal disease is much more common than has

been previously recognized.

After recognition and treatment of urinary tract infection in pregnancy, careful followup examinations are important. If the infection continues, urological evaluation is mandatory. Voiding cystourethrography and urethral calibration are valuable supplements to the generally accepted radiographic and endoscopic means of measuring the function of the urinary tract.

Previously unrecognized abnormalities of the urethra and ureteral reflux are being recognized, and every case of persistent urinary tract infection in pregnancy requires a careful urological evaluation.

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Hippocrates

Before Hippocrates, medicine was in the hands of priests. The priests thought diseases were caused by demons and angry gods, which still sounds pretty plausible. But Hippocrates thought sickness could be traced to natural causes, such as bad diet, lack of fresh air, too much carousing around, and falling off the top of the Parthenon.

"In truth we know little or nothing about Hippocrates," says one historian, preparatory to writing of him at length. It seems Hippocrates was born in 460 B.C. and lived until about 355 B.C., which, if our subtraction is correct, made him 105 years old at the time of his death. His ability to keep himself alive so long must have been one reason he gained the confidence of his patients.

There are some fascinating legends about Hippocrates. One is that he never gave a thought to money. Another is that he admitted his errors. The reader should keep in mind that these are legends.*

*Richard Armour: It All Started with Hippocrates, 1966.

A Meeting of the Committee

Having served on various committees, I have drawn up a list of rules. Never arrive on time; this stamps you as a beginner. Don't say anything until the meeting is half over; this stamps you as being wise. Be as vague as possible; this avoids irritating the others. When in doubt, suggest that a subcommittee be appointed. Be the first to move for adjournment; this will make you popular; it's what everyone is waiting for.—Harry Chapman



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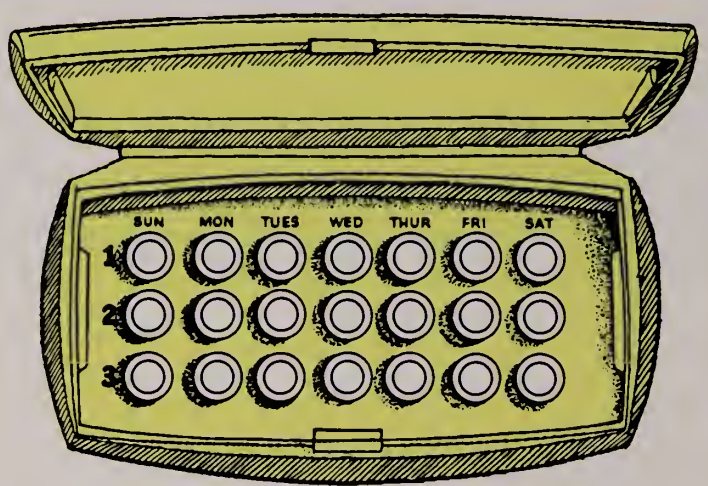
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Special note: Oral contraceptives have been marketed in the United States nce 1960. Reported pregnancy rates vary from product to product. The effecveness of the sequential products appears to be somewhat lower than that of e combination products. Both types provide almost completely effective conaception.

An increased risk of thromboembolic disease associated with the use of horonal contraceptives has now been shown in studies conducted in both Great ritain and the United States. Other risks, such as those of elevated blood pres-ıre, liver disease and reduced tolerance to carbohydrates, have not been quantated with precision.

Long-term administration of both natural and synthetic estrogens in subpriate animal species in multiples of the human dose increases the frequency of me animal carcinomas. These data cannot be transposed directly to man. The ssible carcinogenicity due to the estrogens can be neither affirmed nor refuted this time. Close clinical surveillance of all women taking oral contraceptives ust be continued.

Indication—Demulen is indicated for oral contraception.

Contraindications—Patients with thrombophlebitis, thromboembolic disorders, erebral apoplexy or a past history of these conditions, markedly impaired liver nction, known or suspected carcinoma of the breast, known or suspected strogen-dependent neoplasia and undiagnosed abnormal genital bleeding.

Warnings—The physician should be alert to the earliest manifestations of rombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary mbolism and retinal thrombosis). Should any of these occur or be suspected e drug should be discontinued immediately.

Retrospective studies of morbidity and mortality in Great Britain and studies morbidity in the United States have shown a statistically significant associaon between thrombophlebitis, pulmonary embolism, and cerebral thrombosis nd embolism and the use of oral contraceptives. There have been three princiıl studies in Britain[1-3] leading to this conclusion, and one[4] in this country. The timate of the relative risk of thromboembolism in the study by Vessey and oll[3] was about sevenfold, while Sartwell and associates[4] in the United States ound a relative risk of 4.4, meaning that the users are several times as likely to ndergo thromboembolic disease without evident cause as nonusers. The merican study also indicated that the risk did not persist after discontinuation administration, and that it was not enhanced by long-continued administraon. The American study was not designed to evaluate a difference between oducts. However, the study suggested that there might be an increased risk of romboembolic disease in users of sequential products. This risk cannot be uantitated, and further studies to confirm this finding are desirable.

Discontinue medication pending examination if there is sudden partial or mplete loss of vision, or if there is a sudden onset of proptosis, diplopia or igraine. If examination reveals papilledema or retinal vascular lesions medicaon should be withdrawn.

Since the safety of Demulen in pregnancy has not been demonstrated, it is commended that for any patient who has missed two consecutive periods regnancy should be ruled out before continuing the contraceptive regimen. If e patient has not adhered to the prescribed schedule the possibility of pregncy should be considered at the time of the first missed period.

A small fraction of the hormonal agents in oral contraceptives has been idenfied in the milk of mothers receiving these drugs. The long-range effect to the ursing infant cannot be determined at this time.

Precautions—The pretreatment and periodic physical examinations should inude special reference to the breasts and pelvic organs, including a Papanicoou smear, since estrogens have been known to produce tumors, some of them alignant, in five species of subprimate animals. Endocrine and possibly liver nction tests may be affected by treatment with Demulen. Therefore, if such sts are abnormal in a patient taking Demulen, it is recommended that they e repeated after the drug has been withdrawn for two months. Under the inuence of progestogen-estrogen preparations preexisting uterine fibromyomas ay increase in size. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam adequate diagnostic measures are indicated. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. Any possible influence of prolonged Demulen therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving Demulen therapy. The age of the patient constitutes no absolute limiting factor, although treatment with Demulen may mask the onset of the climacteric. The pathologist should be advised of Demulen therapy when relevant specimens are submitted. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids.

Adverse reactions observed in patients receiving oral contraceptives—A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions: thrombophlebitis, pulmonary embolism and cerebral thrombosis.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, breast changes (tenderness, enlargement and secretion), change in weight (increase or decrease), changes in cervical erosion and cervical secretions, suppression of lactation when given immediately post partum, cholestatic jaundice, migraine, rash (allergic), rise in blood pressure in susceptible individuals and mental depression.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: anovulation post treatment, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption and itching.

The following laboratory results may be altered by the use of oral contraceptives: hepatic function: increased sulfobromophthalein retention and other tests; coagulation tests: increase in prothrombin, Factors VII, VIII, IX and X; thyroid function: increase in PBI and butanol extractable protein bound iodine, and decrease in T^3 uptake values; metyrapone test and pregnanediol determination.

References: 1. Royal College of General Practitioners: Oral Contraception and Thrombo-Embolic Disease, J. Coll. Gen. Pract. *13*:267-279 (May) 1967. **2.** Inman, W. H. W., and Vessey, M. P.: Investigation of Deaths from Pulmonary, Coronary, and Cerebral Thrombosis and Embolism in Women of Child-Bearing Age, Brit. Med. J. 2:193-199 (April 27) 1968. **3.** Vessey, M. P., and Doll, R.: Investigation of Relation Between Use of Oral Contraceptives and Thromboembolic Disease. A Further Report, Brit. Med. J. 2:651-657 (June 14) 1969. **4.** Sartwell, P. E.; Masi, A. T.; Arthes, F. G.; Greene, G. R., and Smith, H. E.: Thromboembolism and Oral Contraceptives: An Epidemiologic Case-Control Study, Amer. J. Epidem. *90*:365-380 (Nov.) 1969.

OA1

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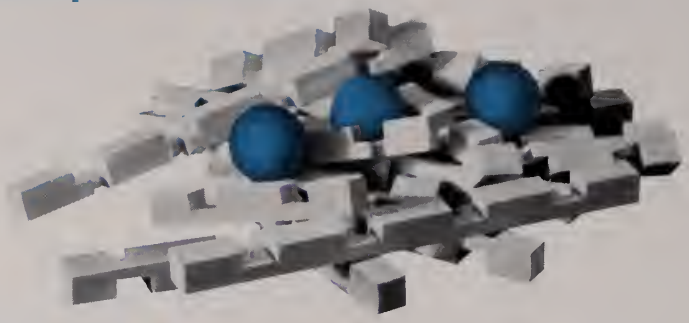
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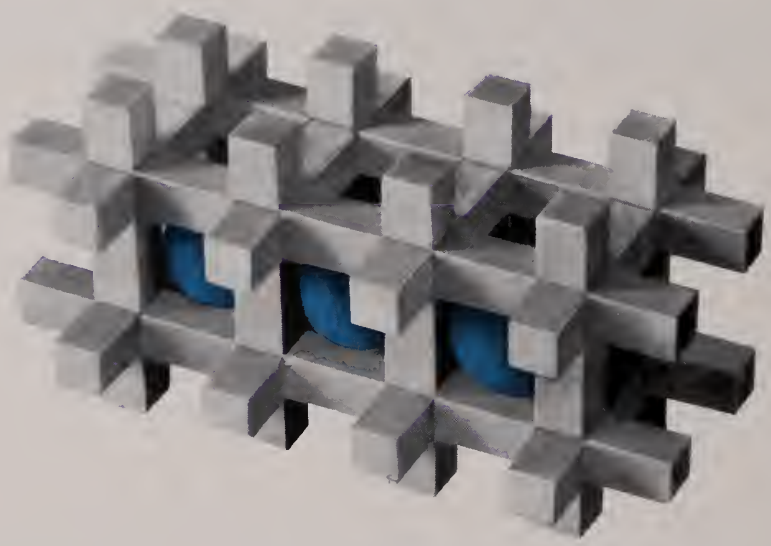
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References: (1) Sands, R.X.: New York St. J. Med. 61:2598-2602, 1961: (2) Renner, M.J., et al: Hosp. Topics 39:71-73, 1961: (3) Haas, Jr., J., and Kay L.L.: Southwest. Med. 42:30-32, 1961 (4) Marshall, W.: Clin. Med. 7:499-502, 1960: (5) Strauss, B.: Clin. Med. 4:307-310, 1957.

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Editorials

If Doctor Hippocrates Calls, Tell Him Minnesota Medicine Is Dying

If he asks why, tell him the decline started with a chill in Duluth. And tell him you expect a downhill course characterized by deficits.

I'm telling you this because I thought you would be concerned.

I am, too.

You see, a month ago, I wrote an editorial called "Quality" in Minnesota Medicine. Then, two weeks ago, on May 19, the chill came on when the House of Delegates of the Minnesota Medical Association voted in Duluth to cut the budget of Minnesota Medicine from $40,000 to $25,000 a year.

Though you may disagree, I think the editorial and the vote are related. As I see it, the House of Delegates killed any hope of our Association maintaining a quality medical journal.

Oh, it's true Minnesota Medicine can skimp and limp along with a lackluster cover, poorer grade paper, shriveled contents, fewer original articles, and second-rate editing, staffing, and printing.

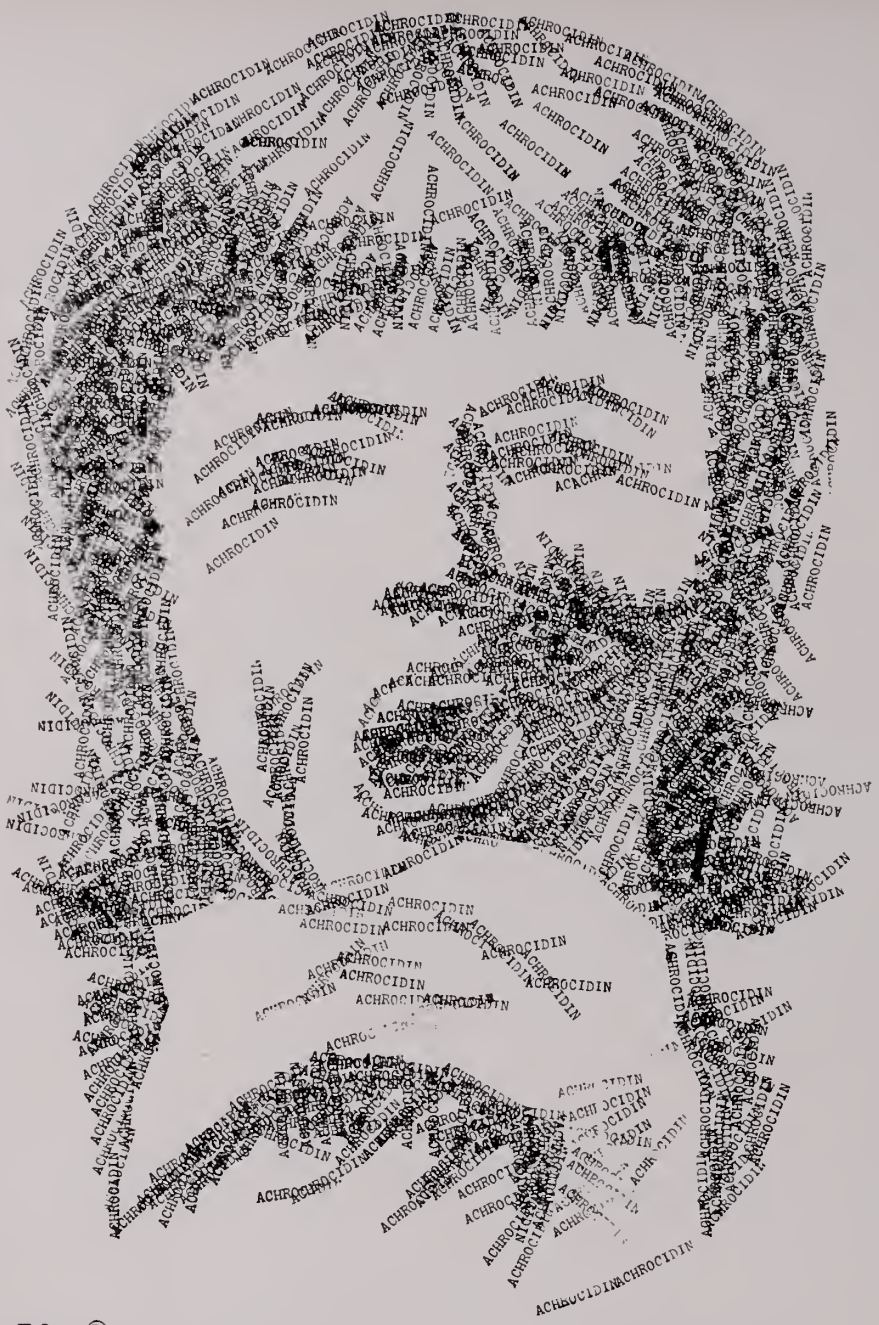
If that's what you want, that's fine. Maybe I'm just being a fussbudget. After all, you publish the Journal through a small portion of your dues (now $14.46 of the $100 you pay; next year, $7.50 of the $125 you pay). So the Journal ought to mirror your attitudes, your interest in the politics of medicine, your level of practice, your concern with ethical standards, and your collective intellect.

I suppose the term "collective intellect" strikes you as a bit highsounding. Perhaps it is. But it's my feeling that the public and physicians in other states hold us in high regard because of our minds—not our political prowess, not our ethical effusions, and not our economic concerns.

In 1963, if you recall, the American Medical Writers Association selected Minnesota Medicine as the best State Medical Journal. The Journal has improved since then, but the Medical Writers Association no longer gives an award for the outstanding state journal. Quite an honor, considering the relative smallness of our Association. In 1967, Doctor John O. Wilson, then of the Midwest Research Institute in Kansas City and now of Yale, ranked Minnesota *first* among the 50 states in quality of medical care offered to its citizens.

It seems the better a collective group of physicians write, the more likely they are to think clearly, and the more their patients will benefit. Anyway, the title of Doctor Wilson's treatise, "Quality of Living," caught my fancy, and, as one of the Board of Editors of Minnesota Medicine, I was proud to be part of an enterprise in excellence.

You probably gather that I think the House of Delegates erred. You're right. I don't see how you upgrade the quality of a State Association by cutting the budget of its Journal, even if you disapprove of the Journal. To me, it's bad politics, bad ethics, and bad communication. I'm not even sure it makes good economic sense since we pay the lowest dues



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Precautions: Drowsiness, anorexia, slight gastric distress can occur. In excessive drowsiness, consider longer dosage intervals. Persons on full dosage should not operate vehicles. Nonsusceptible organisms may overgrow; treat superinfection appropriately. Treat beta-hemolytic streptococcal infections at least 10 days to help prevent rheumatic fever or acute glomerulonephritis. Tetracycline may form a stable calcium complex in bone-forming tissue and may cause dental staining during tooth development (last half of pregnancy, neonatal period, infancy, early childhood).

Adverse Reactions: *Gastrointestinal*—anorexia, nausea, vomiting, diarrhea, stomatitis, glossitis, enterocolitis, pruritus ani. *Skin*—maculopapular and erythematous rashes; exfoliat dermatitis; photosensitivity; onycholysis, n discoloration. *Kidney*—dose-related rise BUN. *Hypersensitivity reactions*—urticar angioneurotic edema, anaphylaxis. *Intracran* —bulging fontanels in young infants. *Teet* yellow-brown staining; enamel hypoplas *Blood*—anemia, thrombocytopenic purpu neutropenia, eosinophilia. *Liver*—cholestasis high dosage.

Upon adverse reaction, stop medication a treat appropriately.

of any State Medical Association members in the Upper Midwest.

In these times, the main job of this Journal will be to keep physicians talking to each other in the same language. As we become more specialized, more clinically isolated, and more ensnared in the government's web, talking to each other is going to be important. A quality journal is the best place to carry on such talk, if it's going to have any dignity and class. Because, while we're talking, we can also record what's new, educate each other, and provide a forum for open discussion.

But maybe you don't want open discussion—in print. Maybe you can achieve the same ends behind closed doors at medical meetings. Or maybe coffee chatter at hospital staff rooms, meaty morsels in newsletter releases, or tangy letters in national journals will do the job.

I doubt it. Talk is perishable; print is not. Besides, newsletter releases are generally badly done. And you simply don't use correspondence columns of widely read journals—JAMA, NEW ENGLAND JOURNAL, or specialty publications—as a media for exchanging ideas or for publishing articles. Not unless you're fortunate. You're lucky if you get a letter published; you're among the privileged few if your paper passes editorial muster in overcrowded national journals.

I'm saying you need MINNESOTA MEDICINE. It's an extension of your minds and your prestige. If you cut its funds nearly in half in a time of inflation, it will cease to grow. And, along with the things it represents, it will die a little each day.

Richard L. Reece, M.D.
Minneapolis, Minnesota

A Glimpse of What We Have Seen*

THERE WERE 174 of us first licensed to practice medicine in Minnesota in 1920. Our 23 (13 per cent) remaining members who now have the privilege and the honor of joining the 50-Year Club pay tribute to and recognize the splendid contributions and achievements of those who have passed on.

Fifty years is more than 71 per cent of the present span of human life. To that must be added eight or more years of premedical and medical training, making a total of approximately 1,334 years (82 per cent) of the lives of our 23 members which have been devoted to the medical profession.

We have lived through a period when more has been accomplished for the health of people than had formerly been attained throughout mankind's known existence. A considerable part of the achievement during our time was made possible by agents and knowledge previously acquired. For example, the cause of many bacterial diseases had been determined during the last century and a few specific diagnostic procedures had been established. However, it was during our time that they were used most effectively.

Small pox was known to be caused by a specific filterable virus and a preventive measure had been available since 1798. In 1924 there were 3,125 cases and 307 deaths. This apparently awakened the profession and the public to the importance of vaccination so that by 1944 only one case and no death were reported. The last case in Minnesota occurred in 1961.

When our 50-Year Club members began practicing, 684 cases and 71 deaths from *typhoid fever* were reported in Minnesota. However, only two cases and no death occurred in 1968.

Poliomyelitis was also a serious challenge during our 50 years, with 702 cases and 102 deaths in 1921. The last case was reported in 1966 but no death has occurred since 1962.

In 1920, 7,673 cases and 159 deaths occurred from *measles*. The number of cases reached 29,759 with 66 deaths in 1935; but in 1968, only 20 cases were reported.

There were 4,841 cases and 2,157 deaths due to *tuberculosis* in 1920; but in 1968 only 377 cases and 53 deaths, mostly among elderly persons, were reported.

In 1920, 3,616 cases and 243 deaths were caused by *diphtheria;* in 1968 there were 16 cases but no death.

Our 50-Year Club members watched the results of Doctor Domagh's laboratory in producing prontosil which was followed promptly by the synthesis of a large number of related compounds, some of which were effective in

*See page 765.

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treating infections. We also watched the work of Sir Alexander Fleming in 1928, leading to the production of penicillin; 10 years later we learned of the work of the Oxford group of scientists who demonstrated its values, leading to the industrial production of penicillin both in England and in the United States.

The compound microscopes we used in 1920 magnified objects about 1,000 times; nevertheless, it was that instrument that revealed a new world of organisms including pathogenic bacteria not previously seen by man. Gordon H. Scott, who was trained in Anatomy at the University of Minnesota, built the first electron microscope used in the United States in 1934. Present-day electron microscopes magnify from 100,000 to 200,000 times, making cells of various organs appear so large that they can be dissected to reveal information that could not have been dreamed of in 1920.

The electron microscope has revealed another new world of living objects far below the range of the compound microscope. The number of viruses that have been identified is almost incomprehensible; however, among those which have been identified as causes of diseases such as poliomyelitis, measles, mumps, and rubella, phenomenal accomplishments have been achieved. Thus the immediately past decade has been referred to as the antiviral era; the profession has witnessed a "great breakthrough in the field of medicine." Virologists are agreed that the preparation of vaccines to protect people against virus diseases is one of the largest and most complex problems in medicine. The common cold alone may be caused by one or more of 120 different viruses.

We have seen the achievements of cardiac surgery, organ transplantation, and numerous other contributions. All that has been developed in our time has contributed not only to increasing the span of human life from 43.3 years in 1920 to approximately 68 years, but also to man's increased happiness and efficiency.

Although we have come close, we have not eliminated the cause of a single disease (last case of small pox in 1961) primarily because of complacence which has developed as the eradication goal has been closely approached. It is possible for present and future physicians to eradicate several diseases, just as veterinarians have done with some animal diseases.

Each recipient of the honor of membership in the 50-Year Club is most thankful to our County Societies and State Medical Association for the many privileges and the assistance granted us. We have tried to be:

"Like a hick'ry cog
In the old mill wheel
Each did his part
As his turn came 'round."

J. Arthur Myers, M.D.
Minneapolis, Minnesota

Myelomeningocele*

Our knowledge of the etiology of myelomeningocele has progressed only modestly in the past decade in contrast to the more dramatic scientific breakthroughs in other areas. Perhaps one of the more interesting facts which has emerged in the study of this and other embryopathies is the discovery by Dr. Joseph Warkany of Cincinnati that pregnant laboratory animals can be made to produce litters of young with this defect if the mother is treated with high doses of salicylates and other drugs at precise periods during gestation. Having a laboratory model available fulfills the primary requirement in the systematic examination of birth defects such as myelomeningocele, and provides direction for further investigation.

In the meantime, the management of patients with this problem remains a difficult and costly one. The establishment of clinics designed to provide centralized multi-specialty care for these children can eliminate numerous separate trips to see the neurologist, orthopedist, urologist, etc., and provide high-quality care with maximum conservation of the patient's time and money as well as good continuity.

James F. Mellinger, M.D.
Rochester, Minnesota

*Bunch, Wilton H., and Geist, Robert: Current Concepts in the Treatment: Myelomeningocele. Minnesota Med 53:245, 1970.

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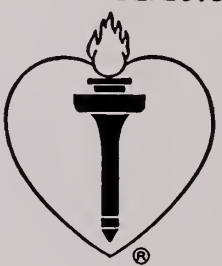
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Howard G. Bruenn was a 39-year-old Naval reserve officer on active duty at Bethesda Naval Hospital in 1944 when he first saw his famous patient, President F. D. Roosevelt. His case report in the April 1970 annals of internal medicine, I think, will be a classic of its kind.

His report indicates that heart failure was present unequivocally when Bruenn first saw his patient on March 27, 1944. Cough was the prominent symptom. There was slight fever (99), tachypnea, and dyspnea almost at rest. Rales were present. The heart was big, and there was a systolic murmur. The blood pressure was 185/108 mm. T1 was inverted. The chest x-ray showed "considerable increase in the size of the cardiac shadow." Could anyone doubt that President Roosevelt had heart failure and urgently needed digitalization? Bruenn had no doubt, but the President was not immediately digitalized "because of the exigencies and demands on the President." A distinguished committee apparently rejected Bruenn's simple advice and specific therapy was deferred.

The touchstone for treatment of the hero is whether or not it would meet standards for care of the indigent. In other words the great man should get at least as good care as the tramp off the street. Unfortunately "exigencies and demands" may preclude this.

Reuben Berman, M.D.
Minneapolis, Minnesota

*The execution was on the charge of attempted poisoning of her majesty.

The Painful Limb (Reflex Sympathetic Dystrophy?)*

A century ago the term "causalgia" was coined to describe the severe burning pain which occasionally occurred in the limbs of American Civil War casualties who had suffered nerve injuries. Subsequent world and regional conflicts have provided ample opportunity to study the effects of injury to peripheral nerves. Approximately 10 percent of such injuries are followed by a characteristic syndrome. It occurs most often in partial lesions of the median or sciatic nerves or brachial plexus. There is always some evidence of motor and sensory deficit in the appropriate distribution. The pain usually begins in the first few weeks after injury; it is always in the distribution of the injured nerve but may radiate to involve larger areas. The pain is usually severe and spontaneous but may be exacerbated by any stimulus to the limb, or even by auditory, visual, or emotional stimuli. The denervation usually results in muscle atrophy, loss of subcutaneous tissue, and development of smooth, thin, shiny skin, and it is often accompanied by osteoporosis and joint contractures. The pain usually subsides in four to five months and rarely lasts more than one year.

The mechanism of development of this syndrome is still unknown. It has been postulated

*See Pak, Tai et al.: Reflex Sympathetic Dystrophy. Minnesota Med 53:507, 1970.

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that, at the site of nerve injury, artificial synapses may be established between efferent sympathetic fibres and afferent sensory fibres. In this way, efferent sympathetic impulses could stimulate or generate activity in afferent sensory fibres, resulting in pain. This would provide one explanation for the relief of pain which frequently follows sympathetic block or sympathectomy, the treatment of choice in cases of persistent severe pain.

Unfortunately for both patients and their physicians, pain as well as soft tissue and bony changes of a similar nature may occur after injuries to non-nervous tissues in the limbs. These conditions have acquired a variety of labels including causalgic states, minor causalgia, Sudek's atrophy*, and shoulder-hand syndrome, and are sometimes lumped together under the term "reflex sympathetic dystrophy." The article by Pak et al. attests to the fact that patients with such symptoms continue to present themselves for diagnosis and treatment.

It appears likely, however, that these miscellaneous conditions should not be considered mere variants of true causalgia, as defined above. The common factor in those conditions without evidence of nerve injury appears to be the initial painful injury or event which results in immobilization of the affected limb. It is probably of some significance that virtually all of the so-called "trophic" and vasomotor changes of reflex sympathetic dystrophy (edema, cyanosis, excessive sweating, joint stiffening and pain, and osteoporosis) may be readily induced by mere immobilizaton and, to some extent, reversed by mobilizing the limb. This probably accounts for the high success rate in treating these patients with active physical therapy. Why sympathetic block or sympathectomy is occasionally effective in cases without nerve injury is unknown.

Arthur C. Klassen, M.D.†
Minneapolis, Minnesota

*See Test Your Word Score below.

†Department of Neurology, University of Minnesota Hospital.

Test Your Word Score

Kreb's cycle—*the tricarboxylic acid cycle* (Page 721).

Arginine—*a crystalline basic amino acid obtained from the decomposition of proteins* (Page 723).

Discutient—*causing a disappearance* (Page 729).

Akathisia—*a psychosis marked by morbid fear of sitting down, resulting in inability to sit still* (Page 731).

Sudek's atrophy—*acute bone atrophy occurring at the site of injury or inflammation* (Page 753).

Lacedaemonians—*the Spartans of ancient Greece* (Page 770).

Polymer—*a compound, usually of high molecule weight, formed by the combination of simpler molecules* (Page 773).

Vasculitis—*inflammation of a small vessel* (Page 789).

Autologous—*occurring naturally or normally in a tissue or structure* (Page 802).

Cytogenic—*pertaining to the origin and development of cells* (Page 810).



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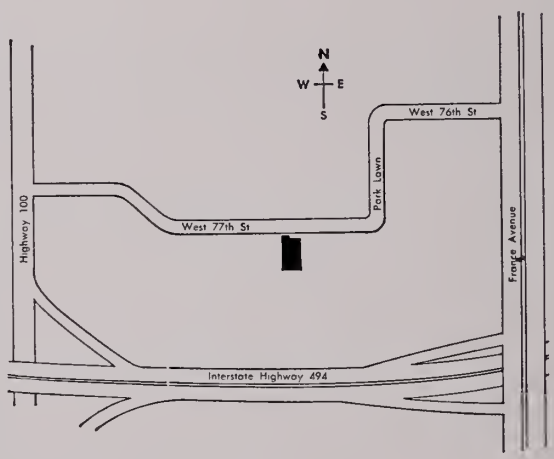
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From 1963 to 1965, the average number of therapeutic abortions performed in United States hospitals (prior to recent liberalization by 10 states) was 2/1000 live births. Eighty percent were done in private hospitals and 20% in municipal hospitals, suggesting that abortions are more available to the affluent than to the charity patient. The medical profession in the United States has been very conservative in interpreting the abortion laws and most hospitals require a very careful review of each applicant.

In Britain, Eastern Europe, Japan, Norway, and Sweden where induced abortion is legal we are being provided the first reliable data on the effects of legalized abortion. It is apparent that these countries are effecting a marked reduction of criminal abortion (78% reduction in Sweden). In Britain 300 women a week are pouring in from the United States and Europe. This has resulted in black-market prices, lack of supervision, and inferior standards of medical care. It is true that problems have arisen following liberalization of abortion laws, but these new problems constitute no argument against the justification for liberalization itself.

It was just two years ago at the first meeting of the Minnesota State Medical ad hoc Abortion Committee that we hesitantly suggested repeal of Minnesota's abortion law. Our appeal to the legislature for statutory reform failed last spring, but ten other states have now modified their laws and many legislatures are considering changes.

We are in the midst of a very rapid social change. The polls reveal that public opinion has changed regarding abortion laws, and public opinion ultimately molds the law. In view of the two recent state supreme court decicions (Belous in California and Gezell in Washington, D. C.), whereby those states' abortion laws were declared unconstitutional, it is possible that change for all states will come quickly via the Supreme Court of the United States. Public opinion is pressuring for *repeal now*, not merely reform in the next 20 to 30 years.

Failure to assume responsibility is shown in a statement from the Minnesota State Medical Association Council, December 19, 1968:† "If (abortion) legislation should be introduced in the 1969 session of the Legislature which is not medically oriented, the Minnesota State Medical Association will take the position that such bills raise social and economic issues with respect to which the medical profession has no special competence and with respect to which it has not, therefore, taken any position."

Fifty-two girls, 14 years and under, were delivered of term pregnancies that same year in Minnesota, but the State Society would take no position on interfering with those pregnancies. Three deaths due to criminal abortion occurred in one week, but yet the State Society could take no stand to help correct the social evils causing those deaths!

Medical training is constantly directed toward the preservation of life.

*As presented at the Work-Shop on Therapeutic Abortion, Minnesota Council for the Legal Termination of Pregnancy, November 21, 1969.

†Bulletin of guide lines in the association's legislative program at the 1969 Minnesota Legislature.

The Doctor

One of the doctor's most important roles is in education.

For his patients, the doctor provides the facts, supplies the rationale, triggers the action for life-saving health practices. To his students, he passes on his knowledge and the benefits of his clinical experience. With his colleagues, he shares new information and concepts.

Assisting the doctor in his teaching role is a major function of our professional education program. Through medical conferences, films, exhibits, pamphlets, monographs and other publications, we provide him with the most important and current information on cancer.

If, as Henry Brooks Adams speculated, "A teacher affects eternity; he can never tell where his influence stops", the outlook is optimistic.



An examination of the last edition of Williams' Textbook on Obstetrics, commonly used in the medical schools, reveals the following statement in regard to therapeutic abortion: "Since therapeutic abortion entails destroying the fetus it is a grave undertaking and must never be considered unless there is imminent danger of death of the mother as the result of pregnancy, or of great bodily or mental harm. Neither the law nor medical ethics permits the procedure for sociologic reasons, i.e., illegitimacy, poverty, or rape."

There is a certain moral rigidity in the doctor of medicine. His attitudes are fixed, his habits ingrained. The church wields an important influence in his life, as well as does the law. Many doctors will not change their perspective until the laws, both secular and religious, are changed. The whole subject of abortion is a distasteful and disturbing subject, and medical specialists in unrelated fields find it something with which they do not wish to become concerned. When a doctor *does* become involved, he may envision his medical ethics and professional ability to be open to question.

If a doctor received medical training, prior to antibiotics, emphasizing the dangers of foreign bodies in the uterus producing pelvic infection, it is very difficult for him to accept the current use of the intrauterine device. If he has been trained since youth that surgical interruption of pregnancy is illegal it is difficult to think otherwise. Illegality is often confused with immorality, which is a matter of opinion. Teenage pregnancies and out-of-hospital abortions, two of the most serious social ills of the community, are matters of *fact*. They are not matters of morality.

Accurate statistics regarding this problem are difficult to obtain, frequently inaccurate and misleading. Very real are the 52 girls, 14 years and less, who were forced to deliver term pregnancies last year in Minnesota.

There are many who argue that legalization of abortions will cause an increase in sexual promiscuity and destruction of the sanctity of marriage. Our society is experiencing a great increase in sexual promiscuity; but we should remember that a mechanistic control of society's morals is of little worth. It is only by augmenting man's freedom that we can increase the spiritual strength of our society.

Another common objection cited to the legalization of abortion is that abortion violates the reverence for life. I am personally not concerned as to whether life begins with the two-cell, four-cell, or eight-cell division but I *am* extremely concerned with the quality of life which will result from the division. We should be more concerned with the welfare of living teenagers and women than with the future of a few embryonal cells.

With the advance of medical progress, doctors have to consider more than merely saving lives; they must also consider the quality of lives ("total environment, actual or reasonably foreseeable"*). It is to improve the quality of life that church leaders have become active in the abortion reform movement. Some outstanding church men have now organized to help bring proper medical services to abortion victims where the medical profession themselves have done little or nothing.

But we've come a long way in our thinking in the past year. Our arguments in appealing to the legislature only one year ago were to the effect that this was a medical problem and that, therefore, the decision should be made within the medical circle of a five-doctor committee. But it is apparent that the problem is much broader than that. The problem is primarily a social-moral one, involving human civil rights, towards which public opinion is rapidly changing. Let us all work to remove an archaic law from our statutes!

Jane E. Hodgson, M.D.
St. Paul, Minnesota

*World Health Organization in defining health in relation to environment.

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Editor's Soliloquy

Archeological Friends

"How old are you?"

"Because I won't tell, my archaeological friends are in the process of determining my age through the medium of carbon dating. They tried a few other archaic dating processes, all of which proved too unreliable. I'm about as old as I feel! I am not yet 'spry,' though that would date me pretty accurately, for certainly a man is not 'spry' until he begins to falter. It may be all a matter of perspective, or perhaps of relativity! To my teenage daughter I was pretty old at 40, but to my teenage grandchild I am almost ancient. They've pegged me though, in the cycle of history: Adam and Eve, the Mayflower Pilgrims, George Washington, Abraham Lincoln and now me. I enjoyed their contemporary association of me with great characters of the past and just let it stand as an index of their love.

"My yard man who inquired, 'Got all your teeth yet, Doc?' was no doubt dating me by the equine method. My internist, on the basis of my electrocardiogram and the step test, categorized me as possessing the reserve of a young man; and my orthopedist, in a gracious moment, gave me a very generous dating when he saw those spurs on the x-rays of my spine and called them physiologic. My dermatologist was much less kind, however, when he referred to the wart on my chin as a senile keratosis; but a classmate of mine who had not seen me for many years (with a white lie in his heart and a mental reservation) maintained that I didn't look a day older than when we graduated. Bless his soul!

"I'm old enough to vote, but not too old to make my own decisions; old enough to go to bed at a reasonable hour, but not too old to enjoy a late party; old enough to take an occasional drink, but not old enough to 'need' it for medicinal purposes; too old to be exercised over the dissidence of youth, but not old enough to disregard the current devastating syndrome of inflation, pollution, corruption and war without resisting; too old to be rebellious but too young to be apathetic; too old to be mendacious but not old enough to admit my age; too old to care to continue the 'rat race,' but too young to care to retire; old enough to assess the past, but young enough to essay the future; old enough to be an introvert by the fireside, but young enough to be an extrovert on the ski slope.

"I'm quite sure I'm about as old as I look. When my wife becomes upset with me she tells me that I must have been born in the latter part of the last century (whew!), which sounds, even to me, like eons ago."

"Now,—how old are *you*, Sir?"

Carl O. Rice, M.D.

OLD DOC HESS SAYS: Reason for having a vasectomy: Too old to become a father, too young to quit enjoying life!

Age

Man weeps to think that he will die so soon; woman, that she was born so long ago.—H. L. Mencken

(Continued from page 713)

pendent private practice. This shift belies the trend that certain social and political commentators say must take place to remedy the woes of a health care delivery system which they claim is failing to adequately meet the prevailing needs by not responding with flexibility and innovation. Newspapers, radio, and television are replete in reporting alleged abuses by health professionals, with a reportorial technique which often holds the physician responsible for the consequences of actions and circumstances over which he may have little influence. This is particularly true since the advent of Medicare and Medicaid Programs where unexpected but predictably high costs have been reported in a skewed manner, charging physicians' fees with the major responsibility for cost escalation and under-emphasizing administrative and hospital costs. The vast majority of physicians are profiting mainly because they are working harder and longer hours due to the increased demand for their services. Inadequate and inaccurate reports concerning the often recondite matters of medical investigation and debate may lead to unnecessary confusion, alarm and distrust by the lay public. All of this adds further insult to the image of the physician who is damned because he lacks the compassion of the horse-and-buggy doctor who sat through the night with his dying patient, but who is also simultaneously confronted with the demand to take care of larger numbers of people with greater efficiency, knowledge and skill by a consumer society whose past gratitude is being replaced by an attitude of indifference and sometimes hostile skepticism as evidenced by an increasing frequency of malpractice litigation.

One might speculate about the causes of the failing image of the physician. Is it really altogether due to the shortcomings, excesses and insensitivities of doctors? I think not! Taken as a whole, doctors today are professionals with as much integrity and altruism as in the past, particularly if the values and standards of the present society are compared with those of the past.

Perhaps the image of the physician is merely a reflection of the image of the society in which he lives. If so, then maybe the public expects him to stand like a Gibraltar against such change and in a paternalistic fashion be a haven of strength to which many may turn with dependent fears when they are under stress but toward which, as toward "the establishment," they turn with hostility and attack when stress reduces as a denial of that dependency. It has long been recognized that some patients may need to relate to their doctors in a distorted but often necessary way as being omnipotent or as parent surrogates. Unfortunately some doctors seem eager to see themselves this way also and nurture their patient's dependency only to frustrate it later when the burden of carrying such responsibility becomes onerous. Then the patient reacts with dismay and often with feelings of rejection and anger.

I have great confidence in the wisdom and responsibility of the press if we can make our case better known to them and they, in turn, to the public. Perhaps this could be achieved by encouraging county and state medical societies to establish public information resources or committees which could speak out authoritatively whenever significant issues, the content of which the medical profession may question, appear in the local news media.

We should continue to question and examine our own motives and behavior—a tradition well understood by a profession conditioned to self-critique through years of mutual evaluation and examination by hospital staff and professional society committee action. Lastly, we should endeavor to become more flexible, open-minded and innovative so that we recognize and seize opportunities to take leadership in developing and structuring new and more adequate systems of health care delivery and not just wait to follow the leads of others.

Efficiency, ease of practice, freedom to work in the best interest of the patient with one's best skills, the challenge of competition and the demands of survival and success which sharpen those skills, earning respect from patient and colleague alike—all are motives which I consider important to good patient care because they deny apathy, indifference, and the sense of futility which is so easily the by-product of bureaucratic, institutional systems. We must work together to design a new system which preserves the freedom and vitality of the physician to serve his patient better in the future.

Donald R. Daggett, M.D.
President
Minnesota Psychiatric Society

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Fifty Years of Faithful Service

Walter G. Benjamin, M.D.

I have been the city health officer in Pipestone, also serving that community and the surrounding area as surgeon for over 40 years; been on the staffs of Ashton Hospital, Pipestone, and Flandreau Hospital, Flandreau, South Dakota. I was a 1921 University of Minnesota Medical School graduate and interned at the University of Minnesota Hospitals and Minneapolis General Hospital and took postgraduate work at the Mayo Foundation in diagnosis and surgery. In addition to my busy schedule as physician in a rural area, I have been active in civic affairs, serving as president of the Pipestone Board of Education and the Pipestone Civic and Commerce Association.

William F. Cantwell, M.D.

I graduated in 1920; spent a short time at Swift & Co., then received an appointment at Mayo Clinic in Rochester.

I wanted to move out on my own and settled in a small northern Minnesota town. After two years, I went east to Chicago, New York and Boston for postgraduate work in surgery. Following this, I located in International Falls.

At first, in this small town, the nearest hospital was 25 miles away. As roads were often impassable I had to use my own judgment and operated on kitchen tables and delivered babies at home. Many people died of pneumonia, infections and other diseases. I had no antibiotics, no vaccines, no insulin, but I did my best with what I had. The successful outcomes have made it worthwhile. Knowing I helped many people and made their lives more livable was enough for me, even though the failures hurt.

Roger S. Countryman, M.D.

Until I retired in 1958, I practiced obstetrics and gynecology in St. Paul. I was born in 1895, graduated from the University of Minnesota Medical School in 1921, and interned at Ancker Hospital and Vancouver General Hospital, Vancouver, British Columbia, Canada. I took postgraduate training at the University of Pennsylvania Graduate School of Medicine, Philadelphia, Pennsylvania, in obstetrics and gynecology. During my years of medical service, I was chief of Obstetrical Free Bed Service at the Charles T. Miller Hospital and director of the Wilder Dispensary Prenatal Clinic.

See editorial, page 747.

Earl R. Crow, M.D.

In 1939 I served as president of the Scott-Carver County Medical Society. I was a general practitioner with a special interest in tuberculosis. I graduated from the University of Minnesota Medical School in 1921 and interned at Minneapolis General Hospital. After internship, I practiced in Green Isle for two years and Minneapolis for four years. I then practiced in Arlington where I became active in the county society before finally moving to Walker.

Della G. Drips, M.D.

I was born in La Crosse, Wisconsin, on September 24, 1884, the daughter of Nellie Emma Gay Drips and Robert Clarke Drips. I received the degree of bachelor of arts in 1907 from the University of Wisconsin. After some graduate work at Wisconsin and four years as a laboratory worker and student at the Mayo Clinic, I entered the University of Minnesota Medical School in 1917, graduating in 1921. I interned in the New York Infirmary for Women and Children in 1920 and 1921, and in 1921 returned to Rochester as a fellow in medicine of the Mayo Foundation.

Even as a medical student, I was keenly interested in endocrinology. My master's thesis dealt with the corpus luteum of the marmot, and I continued my studies in endocrinology at the Mayo Clinic. In 1932 I visited medical centers in Europe where research work in the hormones of the pituitary body, ovaries and uterus was in progress. When I returned to Rochester, I established a laboratory at the Institute of Experimental Medicine for such studies, in association with Dr. Frank C. Mann, Dr. Arnold E. Osterberg and others.

From 1937 until my retirement in 1949, I was physician to the Mayo Clinic Women's Club. On August 14, 1949, members of the club presented me with a silver service in appreciation of my many years of service to the club. In 1951 I was appointed to the Committee on Recommendations for National Legislation of the Business and Professional Women's Clubs, and I was also corresponding state chairman for Minnesota in the field of health and safety.

Since my retirement, I have lived in Oronoco, Minnesota.

Robert E. Fricke, M.D.

What does one do when the mandatory age of 65 forces one to terminate work in his chosen specialty? Minnesota has an ideal climate for winter sports. However, certain sports are regarded with disfavor by those over 65, such as climbing about the roof to chop off ice, or the thrill of sitting down suddenly on ice-slicked pavements.

However, one forms life-long friendship with the splendid people in Minnesota. Also, I wanted to keep in touch with medicine, so I solved my problem by volunteering as executive secretary of my local county medical society, and this has proved most satisfying. My main effort has been to keep my county medical society on good terms with our friendly and paternal Federal Government. Perhaps in the distant future, computers and politicians can diagnose and treat the sick.

On graduating from medical school in Baltimore half a century ago, my main interest was in gynecology. Fortunately I joined the junior staff at Dr. Howard A. Kelly's private hospital. Dr. Kelly had been Chief of Gynecology at the Johns Hopkins Medical School. For seven years I had the opportunity of working daily with Dr. Kelly—the best teacher I have ever known—in this developing area of radium and x-ray treatment of cancer. This changed my interest from gynecology to cancer therapy. In 1927 I joined the staff of the Mayo Clinic in radium therapy and found the same dedicated and cooperative men at the clinic as I had known in the East.

One other tribute I must pay in thanks for a happy life—to my wonderful wife. She taught me to be less argumentative.

Herbert L. Huffington, M.D.

When my colleagues advised me that my health gave me just so much time, and did I want to live it up or stretch it out, I took their advice and retired from practice. After looking around, my wife and I decided on semitropical Brownsville, near Mexico, to live in winters. We find most Latins, who comprise about seventy-five percent of the population, fine people, and they hold positions in high regard in the community. We purchased a home where we enjoy raising citrus and other tropical fruits with the help of a loyal and devoted Mexican family. We brushed up on our Spanish. This made travel into Mexico more interesting. Although speaking Spanish is not essential, it does open up many contacts ordinarily missed down there. Summers find us at our home on beautiful Lake Superior where the foliage is pines, spruce, birch and cedars, instead of palms, bougainvillea, oleanders and other tropical plants. When asked which place we prefer, we find it hard to answer. Among the highlights of the year are our visits with our son, Dr. Herb Huffington and family at Waterville, Minnesota.

Herman M. Juergens, M.D.

Forty-six of my fifty years in the practice of medicine have been in Belle Plaine, Minnesota. Two sons are in medical practice in this state. We also have one daughter and eleven grandchildren.

I was a member of the Committee of Physicians Assistance since its inception, but have recently resigned.

My most memorable and difficult encounter in my years of general practice was the delivery of triplets, all of them having erythroblastosis fetalis. With transfusions, all survived. Enclosed is a recent photograph as requested.

Leroy J. Larson, M.D.

Time takes its toll: changes from a young man to one of advanced age in fifty short years. Some events were sublime, but more were ridiculous.

I recall a few ridiculous episodes such as being called out on a cold winter night, going part way by car but an additional 16 miles by sled with a speed of 3 miles per hour to see an old man who said he wanted to have me come to see him because he wanted to ask me a few questions. "Doc, what happens to the pills I take for my bowels, when my bowels don't move?" Interesting question, wasn't it?

Forty years ago, many calls were made part way by team. I always carried a lantern along with robes to keep me warm. I remember delivering an Indian girl on the reservation. When I entered the small cabin and started to set up my pack and instruments, I saw the patient kneeling on the floor, resting her abdomen on a chair and pressing down vigorously. An older woman said "You better get down there Doc, it's coming." So I got down on my hands and knees to deliver the baby. I felt just like Yogi Berra catching a low ball.

Then there are the incidents of people who were not so alert. I had told a mother to bring the baby in two weeks after delivery for an examination. The father also came and when I said the baby needed to be circumcised, the father said "You cut the cord too long, eh Doc?"

Or the old man who asked me at a social gathering how many cases of "sugar on the brain" I had seen. When I told him I had never heard of it, he informed me that he had it recently and it took his doctor three months to dissolve it. He asked where I went to school, I told him, and he looked at me sorrowfully and walked away muttering, "Never heard of sugar on the brain?"

And also amusing was the woman, age 65, who asked for a prescription for the "pill." I casually asked whom it was for. "Myself," she replied. I told her it was ridiculous for a woman of her age to think she could get pregnant. Her reply: "I don't dare take a chance."

Arthur M. Lundholm, M.D.

I should like to relate a couple of anecdotes from my experiences in the practice of medicine. While I was practicing with Dr. E. G. Sterner, Dr. Zion from North Branch called up and said he had a patient with a ruptured ectopic. We suggested the patient be sent down to St. Paul for surgery. He said that the last train had left and there would not be one until the next day, and the roads were almost impassable.

We then decided to go to North Branch. After getting an anesthetist, sterile surgical instruments and drapes, we proceeded to drive to North Branch. We found we had to operate on the patient in her home. Since the town had no electric lights, we had four men hold up kerosene lights. The patient was then placed on two kitchen tables, the field sterilized and the patient draped. The operation was begun, and since this was in the height of summer there were plenty of insects flying around. I said to Dr. Sterner, "Look at the bugs falling into the abdomen." He replied, "They are used to their own kind here." The patient recovered nicely.

Another amusing incident occurred while I was Deputy Coroner. The police asked me to perform autopsies on four men found dead in a garage. The findings at this time made me ask if they had found any evidence of drinking. They said no, but there was a jug on the table containing a small amount of liquid. I suggested they take it to the laboratory and have it examined for ethyl glycol, which it proved to be. On investigation it was found these men had drained a car radiator and drunk its contents.

John L. Mills, M.D.

Almost all of my professional life has been in Winnebago, Minnesota, a town of 2000 people. Most of this time I was in solo practice. In other words, I was a general practitioner. It was fun, but I had a few headaches. I had wonderful patients or maybe they were just patient with me. Either way, I enjoyed my relationship with them. One elderly lady told me that I had made a lot of calls on her but had not done her any good; so she would return the calls, rather than pay for them.

Another time, I answered the phone at home on a Sunday morning and a woman's voice said, "John, I have used two cans of Drano and haven't had any results yet. What should I do now?" (The local plumber's name, you see, was also John.)

I am still married to the same wife I have always had. We have two daughters and seven grandchildren.

I wish to extend greetings and best wishes to the other members of this year's Fifty Club.

Herman J. Moersch, M.D.

The practice of medicine has been a most gratifying and rewarding experience. It has been a privilege to work with so many wonderful men and women at the Mayo Clinic and elsewhere for so many years. While fortunate enough to receive some cherished honors and election to high office in a number of national medical organizations, the one that probably gave me the greatest satisfaction was to be elected by my associates as President of the Mayo Clinic Staff.

During my years as a medical student, I first became interested in medical education, an interest which has remained with me over the years. On retiring from the Mayo Clinic in 1960, I was appointed Director of Education and Research of the American College of Chest Physicians. This has afforded me the privilege of observing the striking changes that are taking place in the technique of medical education.

Since high school days, I have been very much interested in the outdoors and all forms of sport. These have afforded many happy and contented hours. With increasing years golf remains my chief form of exercise. The companionship of my playing companions remains both stimulating and enjoyable although with years the score seems ever to mount.

In the final analysis, the greatest satisfaction has been a happy marriage and raising two fine sons who have been successful in their chosen field and in turn have raised fine families.

Jay A. Myers, M.D.

I long had a desire to see and converse with a centenarian. An item appeared in a newspaper that Grandma Dunham of Hoka was soon to celebrate her 100th birthday. A year or so later I was invited to hold a clinic in Hoka. On arrival, I asked the superintendent of schools whether he knew Grandma Dunham. He said his family and the Dunham family were close friends. When I told him of my desire to see Mrs. Dunham, he volunteered to take me to her home when the clinic work was finished. We walked up several series of steps to the top of a bluff overlooking the river to Mrs. Dunham's home. He rapped and soon the door began to open slightly. Through a small crack, she saw the superintendent and flung the door wide open. There stood a little old lady leaning on a cane and with a patch over one eye. I hastened to extend my hand and said, "So, you are Grandma Dunham." She answered, "Well, no, but come on in, mother is in the kitchen."

Warner Ogden, M.D.

After various activities in the Solomon Islands during World War II, I settled back peacefully to the usual surgical routines in St. Paul. However, by 1957 I decided that rather than progress slowly into innocuous desuetude, I would seek further adventures.

So I got a six-month job doing and teaching surgery in a mission hospital in India, inland from Bombay in the mountains. There were two good Indian doctors, but they and the hospital were much behind in modern methods; for example chloroform anesthesia, no nasal suction, and inadequate I.V. solutions.

Many unusual cases. All were full of round worms, and many had great mesenteric tuberculous masses (all drink milk from the infected water buffalo), huge tumors, terrible wounds from being gored by the sharp horns of their working bullocks—they frequently arrive holding their intestines in a dirty cloth, and practically all recovered when we stuffed things back in and sewed them up.

Oddest case—A woman arrived with her throat cut from ear to ear by her husband. We gave ether on a mask held over the stump of the trachea, and sutured everything. When she could talk, she refused to charge her husband because the whole episode proved how much he loved her.

Two years later I went on a similar job to Ghana, West Africa, to a good hospital far inland in the bush. Funniest story there—A German woman doctor raised chickens, turkeys and other fowl in a wire mesh enclosure. One night a python got in and swallowed her tom turkey, thereby making said python too fat to get out. He was shot, the dead turkey recovered, cleaned, cooked and eaten: truly a predigested (and prodigious) meal!

Since then I have been slowly retiring, now seeing old patients only if and when they can catch me.

Arthur H. Pedersen, M.D.

I was born and raised in St. Paul and, after my medical education and postgraduate work, I returned to practice there. I was a general surgeon and received my undergraduate and medical education at the University of Minnesota and interned at Ancker Hospital. I did postgraduate work at the University of Minnesota and, after several years of practice, went to Austria to take further postgraduate training at the University of Vienna in 1925.

Willard C. Peterson, M.D.

I am a native of Minneapolis and practiced as a general surgeon. I attended Minneapolis South High School and the University of Minnesota, graduating from the University Medical School in 1921. After interning at Minneapolis General Hospital, I did postgraduate work at the University of Minnesota and Mayo Clinic. Then, from 1922 to 1923, I took residency training at Colonial Hospital, Rochester, before returning to Minneapolis to practice.

Lawrence F. Richdorf, M.D.

I am now a practicing pediatrician. I received my medical education at the University of Wisconsin, Madison, Wisconsin, and the University of Minnesota. I interned at Ancker Hospital and the University of Minnesota Hospitals. My postgraduate work was done at the University of Minnesota and Mayo Clinic. I served as assistant professor of pediatrics at the University of Minnesota Medical School.

Leo G. Rigler, M.D.

Since leaving Minnesota, I have held three post-retirement positions: the first as a Consultant in the Department of Radiology at Cedars-Sinai Medical Center, the second as Executive Director of the Cedars-Sinai Medical Complex, and the third, as a Professor of Radiology in Residence, at the University of California, Los Angeles, a position which I have now occupied for almost seven years, even though I am far beyond the age of retirement. My most important distinction of the past few years was to have been elected to Honorary Fellowship in the British Faculty of Radiologists, and at the present time I am the only living American to hold that distinction. Finally, my wife and I are both extraordinarily fortunate in having had good health and, at the same time, having all our children and our seven grandchildren living in our immediate vicinity. My latest enterprise consists of a Visiting Professorship at the Hebrew University Medical School in Jerusalem and at the Tel Aviv University in Israel to continue for some six months. In fact, we are leaving for this post next week.

John A. Seaberg, M.D.

I was born in Evanston, Illinois, where my father was a student at the Swedish Methodist Church Seminary. My early years were spent in many communities of the Midwest, as is the lot of a minister's family.

After getting a B.S. degree at the University Medical School, I transferred to Northwestern University Medical School. In due time, I received my diploma at the old Patton Gymnasium in the city where I was born.

My active medical story concerns almost entirely the care of veterans. I was on the House Staff at the Asbury Hospital in Minneapolis when it was taken over by the Public Health Service for the care of World War I veterans. It was my pleasure to serve at that time under Dr. H. M. Bracken, Medical Officer in Charge, with a consultant staff of prominent local physicians similar to the one inaugurated by the University of Minnesota at the Fort Snelling Hospital many years later.

Subsequently the veterans' care was placed under the Veterans Bureau, and later the Veterans Administration, and our hospital was designated as V.A. Hospital #68. In 1926 the new Fort Snelling Veterans Hospital was opened, and I was assigned there. Except for a short tour of duty at the V.A. Hospital in Alexandria, Louisiana, and in Washington, D. C., I continued at the Fort Snelling Hospital until I retired in 1957.

Prior to 1944, I was in charge of the Tuberculosis Service. After that I had other administrative assignments, the last six years as Hospital Director.

I consider my association with the beginnings, in 1946, of the University of Minnesota Medical School Residency and Consultant Programs as one of the highlights of my professional career. My association with many of the excellent physicians and also outstanding men who were my colleagues in the Veterans Administration Service in Minneapolis evoke many pleasant memories.

Leon A. Steffens, M.D.

Doctor Steffens (deceased) was a general practitioner, born in Chicago, Illinois. He received his undergraduate education from the University of Chicago in Chicago, Illinois, graduating in 1915. He was graduated from the University of Minnesota Medical School in 1921 and interned for two years—first from 1919 to 1920 at the University of Minnesota Hospitals; the second, from 1920 to 1921 at Ancker Hospital. He practiced in Brooten for a short time before setting up practice in Red Wing.

Harold C. Stratte, M.D.

Besides my rural practice the past 50 years, among my greatest accomplishments was the landing of a forty-pound lake trout with a twelve-pound test line. (Actually when I caught the fish, it weighed thirty-four pounds. I used a copper wire line, but the fish has grown heavier and the line weaker.)

Among my hobbies are listening to music (canned or otherwise), traveling and visiting with my children and grandchildren. Each year I take a salmon fishing trip to the Puget Sound area, digging for clams and gathering oysters.

I do not plan to retire, at least for the next 50 years.

Ruby Veirs, M.D.

Dr. Veirs (deceased) was born in Vernon, Texas; attended Texas Wesleyan College, Fort Worth, Texas, and later was graduated from Southern Methodist University, Dallas, Texas. She became a social service worker in a Mexican settlement house in Fort Worth, taught school in Fort Worth and Waco, Texas, and in Mexico City, Mexico. Later she was graduated from the University of Louisville Medical School and interned in Louisville City Hospital, both located in Louisville, Kentucky. Doctor Veirs held a residency in obstetrics at Fordham Hospital, New York, New York, and then practiced in St. Paul from 1924 until her retirement in 1964. In addition to her private practice, Doctor Veirs assisted in examining patients at the St. Paul YWCA for about 15 years. She was a member of the Pan American Women's Medical Association.

A. Elliott Vik, M.D.

I am a general surgeon and was born in Willmar. I attended the University of Minnesota from which I received my B.S. degree in 1918, my B.M. degree in 1920, and my M.D. degree in 1921. Following my schooling, I interned for two years at City and County Hospital and at Swedish Hospital. Before setting up practice in Minneapolis, I served Big Lake from 1921 to 1923 and Winthrop from 1923 to 1926.

Wilford F. Widen, M.D.

I am still in active surgical practice in Minneapolis. I graduated from the University of Minnesota with a B.S. degree in 1918, receiving my M.D. degree in 1921. I served my internship at Ancker Hospital. After setting up my practice, I became chief examiner in Minneapolis for the New York Life Insurance Company. In earlier years I was an avid tennis player, winning several national honors, including the National Public Parks doubles in 1941 and the national senior clay court doubles in 1950.

Omnivorousness

About the time I was twelve I found the public library. At home we had classics —in the library they had Anger, Henty, Stoddard, Kipling, and also the humorists. One could take out six books at a time. I took six about every five days. Then a rule was made that one could go to the shelves and make selections from them. With my sister's library card I was permitted to take along ten books at a time. Finally a library attendant said: "I suppose you're taking these for the whole family?" "No," I said, "these are for me."*

*Morris Fishbein, M.D., An Autobiography, 1969.

Derivatively Speaking

Gamete—from Greek *gamete* (wife) or *gametes* (husband); from *gamein* (to marry).

Humanities

The Disadvantages of Old Age*

When I consider the various disadvantages which old age is generally supposed to bring with it, I find that they may all be reduced to four general charges. The first is that it incapacitates a man from taking part in the affairs of the world. The second is that it produces bodily infirmities. Thirdly, it disqualifies him for the enjoyment of sensual pleasures. And, lastly, it brings him to the threshold of death.

Old age disqualifies us from taking an active part in affairs. Certainly, insofar as the strength and vivacity of youth are required; but there are public services which can be rendered only in advanced life. Why is our supreme council called the senate, or why is the highest magistracy of the Lacedaemonians† called the Elders, but because age qualifies a man for public affairs, and not disqualifies him?

It is often said that old age impairs the memory; and so doubtless it does in those who have not exercised their faculty. I have not found it so, and I never heard of any aged person who forgot where he had concealed his treasure. Mental powers become blunted chiefly when they are disused. Sophocles wrote tragedies in extreme old age, and I could give many similar instances. Solon used to say that he learnt something new every day. Old as I am, it is only lately that I took up the study of Greek, and you will remember that Socrates learnt to play the lyre when he was past middle life.

The second complaint is that old age impairs our strength, and this, it must be acknowledged, is true enough. But for my part, I no more regret the vigour of my youth than I regretted then that I had not the strength of a bull or an elephant. After all, however, weakness of body is more often the result of dissipations than of long life. If a man be temperate, the decay of his strength will be gentle and not intolerable. Mine has remained sufficient for my duties in the senate and in public assemblies, and for the service of my friends.

We come now to the third disadvantage. Old age is without pleasures. Oh, what an admirable advantage, that we should at length be free from these temptations! I have never forgotten the sayings of the wise Archytas of Tarentum on this point. He said that no more deadly pestilence had been inflicted on man than these physical pleasures; that their insatiable appetite was the source of political treachery and civil catastrophes; and that there was no crime to which sensual passions do not lead. It is from these dangers that old age delivers us, and very grateful we ought to be to old age.

But there remains a fourth reason why men are often filled with anxiety at the approach of old age. Death is coming nearer and nearer. If it means extinction, it is not worth troubling about; if, on the other hand, it means transition to immortality, then it is only to be desired. For my own part, I am transported with impatience to join the society of my departed friends, and to be with other mighty men of the past of whom I have read. To this glorious assembly I am quickly advancing; and if some divinity should offer me my life over again, I would utterly reject the offer. This world is a place which nature never designed for my permanent abode; and I look upon my departure, not as being driven from my home, but as leaving my inn.

*Marcus Tullius Cicero (106-43 B.C.)
†See Test Your Word Score, page 753.

Life

If life had a second edition, how I would correct the proofs!—John Clare

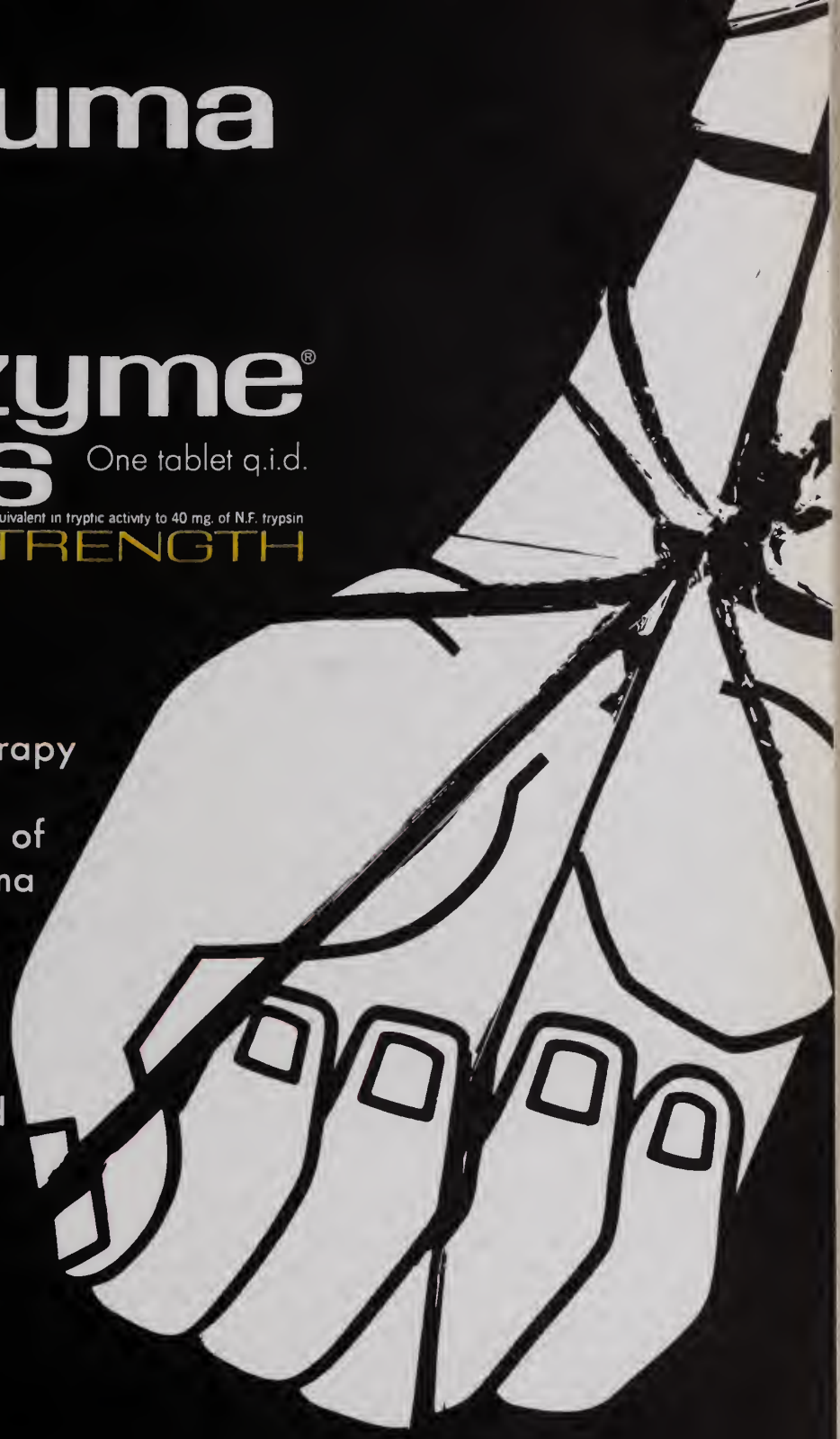
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Biomaterials

Thrombus Formation on Polymeric Materials

I. Interactions of the Biological Environment with Polymers

DOUGLAS A. OLSEN, Ph.D.,* and HAROLD D. KLETSCHKA, M.D.†

MANY OF THE MATERIALS suitable from a structural point of view for use in artificial internal organs were originally developed for uses far removed from the biomedical area. Considerable empirical information is now available on the use of polymers‡ and metals in physiological environments. Correlation of this information, however, into meaningful results is difficult. In the articles to follow we will be concerned chiefly with the compatibility of the materials of construction with blood. By way of background we will first discuss briefly the more general view of the compatibility of implants in the physiological environment of the body.

Effects of the Biological Environment

Various Physiological Effects

Any study of this type quickly shows that the body is a hostile environment for both metals and polymers. The natural response of healing tissue to an implanted foreign body is to encapsulate it in scar tissue. All natural cavities, exposed surfaces, or channels in the body are normally lined with highly specialized tissues adapted to certain roles, e.g., epithelial, endothelial and mucosal surfaces. When the integument or the walls of hollow organs are injured, their repair consists of restoration of structural integrity by connective-tissue-scar formation. However, where scar bridges a gap at an exposed surface, simple connective tissue does not remain bare; it is always covered by new surface tissue which has the histologic characteristics of the adjacent normal epithelium, mucosa or endothelium. These specialized surface "finishes" are the protective coating which permits the underlying, supporting tissues to attain metabolic stability, free from the infection and irritation to which they are susceptible. Such surface tissues halt fibrin deposition, proliferation of granulation tissue and development of more scar.[1] The artificial interface between the inner surface of the fibrous connective tissue which envelops the implanted polymer surface is not a "finished" surface since there is no bond.

The well known immune reaction provoked by the foreign protein of transplanted organs from donors does not seem to be a problem with implanted artificial organs. Davila et al.,[1] however, discuss how an implant partially exposed at the surface of an organ may be rejected because the epithelium will grow into the scar-tissue-implant interface.

The physiological environment of the body can also work drastic physical or chemical changes on the implant. These changes in properties may result from degradation, cross-linking, or phase changes caused by exposure to the aqueous environment or from oxidation by free radical formation and by enzymatic attack.[2] The combined presence of chloride ions and oxygen in tissue or in blood can lead to pitting of stainless steel.[3] Oxygen concentration cells involving stainless steel embedded in bone have also been reported.[3]

Polymer Degradation

That implanted polymers are attacked is demonstrated by the tensile strength data of Table 1.[4,5] Tensile strength, however, is a comparatively crude indicator of change. Label-

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‡See Test Your Word Score, page 753.
Reprints may be obtained at the end of this series from Dr. Olsen at 4106 Linden Hills Blvd., Minneapolis, Minnesota 55410.

TABLE 1
Changes in Properties of Plastic Films after Implantation[5]

Material	Tensile Strength, psi	Elongation, %
Polyethylene		
Control	2,700	780
17 Months	1,930	—
Polytetrafluoroethylene/Teflon		
Control	2,950	320
17 Months	3,720	250
Polyethylene terephthalate /Mylar		
Control	18,300	100
17 Months	18,440	100
Polyhexamethylene adipamide/Nylon		
Control	9,300	550
17 Months	5,200	140
Polydimethylsiloxane/Silastic		
Control	950	800
17 Months	930	890

TABLE 2
Breakdown of Labelled Polymers[5]

Polymer	Time for C^{14} to Appear in Urine, Weeks
Polystyrene	
$(—C_6H_5CH—C^{14}H_2—)$	21
Polyethylene	
$(—CH_2—C^{14}H_2—)$	26
Polymethyl-Methyacrylate	
$(—CH_2C(CH_3)COOC^{14}H_3—)$	54

ing of the implanted polymers with carbon-14 provides direct evidence that the host tissue can break down polymers. Thus, as shown in Table 2, polyethylene gives rise to carbon-14 in the urine within 26 weeks of implantation. Similar results are obtained for polystyrene and polymethylmethacrylate.[3,6] The general effects on polymer properties resulting from exposure to the biological environment have been reported by several authors and are summarized by Lyman[2,7] as shown in Table 3. The varying degrees of reactivity of the several polymers are related to the chemical nature of the polymers. For example, some polyurethane materials degrade rapidly when implanted in rats. These polymers contain a variety of linkages that are susceptible to hydrolysis or enzymatic cleavage

$$(—CH_2OCH_2—,\ —\overset{\overset{O}{\|}}{C}OCH_2—,\ —NH—CO—,\ \text{etc.})$$

and are sufficiently hydrophilic to allow this to occur. Polyhexamethylene adipamide and polycaprolactam also degrade hydrolytically because of their somewhat hydrophilic nature though at a slower rate. In contrast, implanted polyethylene terephthalate, which also

$$\overset{\overset{O}{\|}}{C}$$

contains labile ester linkages ($—COCH_2—$), is relatively stable. This improved stability is due principally to the hydrophobicity of polyethylene terephthalate (water adsorption less than 1%), which prevents water from readily

TABLE 3
Effects of Biological Environment[2]

Polymer	Effect
Polycaprolactam	Only slight absorption over several weeks
Polyhexamethylene adipamide	Loss in tensile strength, degradation
Polyurethanes*	Degradation, softening, loss of tensile strength
Polyethylene terephthalate	No obvious degradation, slight change in tensile properties
Polyacrylonitrile†	No obvious degradation, loss in tensile strength
Polyethylene	No obvious fragmentation or degradation, slight change in tensile properties.
Polymethylmethacrylate	No obvious fragmentation or degradation
Polytetrafluoroethylene	No obvious degradation
Polyvinyl alcohol	Some erosion of sponge, shrinkage, mineralization
Polysilicones	No obvious degradation

*Generic term used for elastic urethane materials; samples examined are not necessarily indicative of all members of this class.
†As a copolymer (Orlon).

getting to the hydrolyzable ester linkages. Bonds of the following types are also eventually attacked by the acids, bases, oxygen, and enzymes of body fluids:[5] -C-O-, -C-S-, -C-N-, -C=C-, and -Si-O-. The supermolecular character of the polymer also needs to be considered:[8] oriented, amorphous, crystalline, folded, crosslinked, etc. Such character does not affect the intrinsic chemical reactivity of the sensitive bonds but influences very profoundly their accessibility and, therefore, the rate of actual degradation.

Degradation has been shown to occur even in polymers that have no reactive sites along the chain and, therefore, should be inert. For example, gross observation of polyethylene showed no apparent changes after several years implantation in rats. However, as noted previously, by using carbon-14 tagged polymers radioactivity was later picked up in the urine, thus indicating that degradation was indeed occurring.[2] Levine[3] also notes that degradation of inert polymers such as polyethylene, which involves cleavage of a carbon-carbon bond by a free radical mechanism, could conceivably be initiated by tissue-free radicals or oxygen. The oxidation-reduction enzymes would appear to be inaccessible to the polymer since they are largely confined to the mitrochondria.

In regard to materials for mechanical heart systems, Akutsu and Kantrowitz[9] have reviewed the available clinical data and conclude that only Dacron and Mylar (polyethylene terephthalate), Silastic (polydimethyl siloxane), and Teflon (polytetrafluoroethylene) are sufficiently resistive to be considered for use. They also note, however, that some alterations have been reported in these materials after 18 to 24 months.

Toxic Effects

Toxic Side Effects

Another aspect that should be mentioned is that implants may give rise to harmful toxic side effects. There are many such reports in the literature. Among the potential dangers are antigenic and toxic phenomena such as reticuloendothelial hyperplasia, hepatosplenomegaly, anemia, ascites, hypertension, or nephritis.[9] Some of these side effects are due, at least in part, to the erroneous assumption of earlier medical researchers that polymers were inert in a biological environment. As an example, Autian[10] cites the differences in toxicity reported for polyvinyl chloride films obtained from several manufacturers and containing differing additives.

Homsey et al.[11] note that the literature on tissue and hematic compatibilities often reports results without including specifics of polymer chemistry, manufacturing source, product identification and identification of preimplantation properties. The lack of such information or procedures for obtaining it have resulted in unwanted side effects in the past. Keith et al.[12] have reported just such a case where the presence of a hemolytic agent in a segment of tubing caused massive hemolysis. Several recent studies have sought to develop methods to evolve screening procedures for candidate prosthetic materials. The procedures have included simulated *in-vivo* stress using pseudo-extracellular fluid[11] and tissue culture tests.[13,14]

Possible Carcinogenic Effects

While such experimental artifacts as toxicity due to additives are now generally recognized, there is still current serious controversy concerning the carcinogenic character of polymers when implanted within the body. A rather large body of literature exists and has been reviewed by Akutsu and Kantrowitz[9] and Halpern.[15] Basically, however, one set of results due to Huepner and Conway[16] show that the chemical nature of the polymer can induce carcinomas. On the other hand, the work of Oppenheimer et al.[17] demonstrates that the state of subdivision is a greater factor in tumor production than the chemical nature of the material itself. The implantation of a continuous sheet results in the formation of more malignant tumors than does a perforated sheet which in turn results in more tumors than sponge, fiber, or powder forms of the same material. Interference with the normal metabolism of the cell and reduced exchange of fluids and gases have been suggested as reasons for this effect.[15] Other possible mechanisms of polymer carcinogenic activity are direct chemical interaction, and microphysical effects,[9] both of which are discussed below.

In the case of direct interaction, degradation products may be the carcinogenic agents. The polymers may be degraded in the presence of

biological free radicals produced by oxidation and enzymatic reactions; then the free-radical fragments arising from degradation may inhibit the enzymatic free-radical process, affect the depolymerization of nucleic acids, and produce tumors. Also, the reactive centers in the polymer itself which are created by the degradation would be capable of binding basic tissue constituents, thereby impairing the metabolism of adjacent cells.[9]

The microphysical effect is seen in metabolically inert macromolecules. Excessive intracellular and extracellular storage of these molecules may interfere with cellular functions in the long run, thereby causing cellular degeneration, cellular death, and further reactive, regenerative cell proliferation.[9]

The most important point in this discussion of carcinogenicity is that the immediate good done by the implant will more than balance the long-term threat of cancer. It should also be borne in mind that carcinogenicity studies are necessarily made on animals that have been bred over many generations to be extraordinarily susceptible to the development of cancer. As Lyman points out, if it takes one to two years for a malignant tumor to appear in a rodent, a similar result may take 10 to 15 years in a human being.[2,7] This may well be a warning against the indiscriminate use of plastics in clinical use, for none of the available materials has been tested long enough to determine carcinogenicity.[18]

On the other hand, the available literature contains no authenticated case of a tumor developed in a human as a result of an implanted material. The list of observed materials contains both purposeful and traumatic implants of many years' duration, such as bullets, broken knives, shrapnel, dirt, wood, glass, silver, plastics such as Teflon, acrylics and Dacron and a wide variety of orthopedic devices.[19]

The Need for Non-Thrombogenic Surfaces

All of the foregoing considerations in regard to compatibility of polymers must be kept in mind for the design of artificial organs. For artificial hearts, lungs, and kidneys plus various other laboratory and clinical devices there is the additional problem of the thrombogenic properties of metals and polymers. These properties will be discussed in much greater detail in the articles to follow. For the present discussion, however, it may be said that any treatment of foreign interfaces which will render them non-thrombogenic will find practical application touching on innumerable biological requirements.

It is conceivable that blood storage may be achieved without the use of anticoagulants. Tubing and containers used for blood transfusions and the administration of other intravenous fluids might utilize non-thrombogenic surfaces without the frequently encountered clotting problems using present day materials. The availability of such materials would permit the long-term use of indwelling catheters (such as in cases requiring continuous intravenous fluids), transducers (for long-term physiological studies for clinical or research use), and electrodes (such as intracardiac pacemaker electrodes). Catheters and/or valves used in ventriculo-venous shunts for hydrocephalus could be fabricated to exhibit enhanced performance characteristics with respect to prevention of blood clotting within the devices. Long-term indwelling vascular catheters such as used for chronic renal dialysis could possibly be left in place without the need for heparin. Needles, syringes, and laboratory bottles, flasks, etc., fashioned from such materials would not only permit the more atraumatic handling of blood, but allow more reliable and meaningful laboratory testing procedures, since artifacts now introduced by way of anticoagulants being added or those produced by alterations in the blood that take place on coming in contact with a foreign surface would be eliminated.

The new materials might also be expected to provide a more satisfactory environment for tissue culture work involving the growth of cellular elements of blood or possibly those also in which blood, plasma, or serum is used as the substrate in which to culture tissue.

It is conceivable that extracorporeal surgery could be carried out without the need for using heparinized blood (either systemically or in the priming blood) with all its attendant risks. Likewise, it seems likely that renal dialysis could be performed without the need for heparinization.

The development of blood-compatible materials would serve to overcome one of the most

formidable obstacles currently preventing the successful development of artificial organs. Among the more feasible are artificial hearts, artificial lungs, artificial kidneys, and artificial placentas.

Improved performance characteristics should be expected for heart valves fabricated from such materials and also for patches used to close intracardiac defects. Improved prosthetics should result for replacement of diseased arteries, and it could be anticipated that prosthetic replacements for diseased veins—for which there is no currently satisfactory artificial material available—would also result. Improved vascular suture material fashioned from polymeric materials could be anticipated.

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The Unborn

"If a human right exists at all, it is the right to be born with normal body and mind, with the prospect of developing further to fulfillment. If this is to be denied, then life and conscience are mockery and a chance should be made for another throw of the ovarian dice.*

*N. J. Berrill, The Person in the Womb, 1968.

Friendship

Be friendly with the folks you know. If it weren't for them, you'd be a total stranger.—New York World-Telegram.

Hunger is sharper than a sword.—Beaumont and Fletcher

Abstract

Communities, Doctors and the University

The Student's View*

Regionalization is the order of the day.

Many communities are facing the prospect of losing their doctors or are already learning to live without them. Most communities express strong interest in a return of the horse-and-buggy country doctor, who knew everyone and was always available. Communities hold their own doctors in high regard, but there is widespread disillusionment with doctors in general and with organized medicine.

The Present

The doctor's life is increasingly hectic, with greater numbers of patients and problems on the one hand and expanding diagnostic and therapeutic knowledge on the other.

The system of rewards, in terms of both prestige and income, serves the interests of the physician who manages the medical catastrophe rather than the physician who averts it.

Public health has been relegated to a position below that of "real" medicine. In short, the medical profession is by and large oriented toward disease rather than health care.

Medical education is still very much disease-oriented, and among students, interns and residents even diseases are ranked. The most prestigious diseases are rare, acute, devastating and responsive to heroic medical management. The non-prestigious diseases are common, chronic, disabling and relentlessly progressive or unresponsive in the face of treatment.

The Future

First, I see the possibility of a health care communiversity. The artificial division that has grown up between the university and the community physician must not be permitted to persist, for it works against the best interests of both. The community physician needs to learn much more of the increasingly complex scientific background of clinical medicine. He must learn how he can contribute to the body of medical knowledge through research, and the university physician must learn how he can use community practice for research.

Second, I see the possibility of physicians assuming responsibility for health care rather than just medical care. A partial list of such professions would include dentistry, mortuary science, nursing, nutrition, psychology and social work. We cannot permit sentimental attachment to disease to stand in the way of physicians providing a more basic service than medical care. I believe the physician of the future will be able to provide more comprehensive health care for more people than he is presently able to do with only medical care. I consider establishment of the Department of Family Practice and Community Health at our university a particularly promising circumstance for our state. There is new emphasis on cooperation in health care and in education, with newly defined goals in both areas. I look forward to joining you all in bringing these goals to realization.

*Extracts from a presentation given by David E. Johnson, 761 Como Ave., St. Paul, Minnesota.

Dermatology

Sporotrichosis

Sporotrichosis is caused by the fungus, *Sporotrichum schenckii,* which exists as a saprophyte on decaying vegetation, soil, or animal excreta. The fungus is usually introduced into the skin by minor trauma such as puncture by a thorn or piece of metal. Adult males who work outside are most susceptible to infection because of their increased chance of exposure. The incubation period varies from three days to three weeks.

Clinically, sporotrichosis may exist in two distinct types. The most common type is the localized lymphatic variety which results from implantation of the spores in an abrasion or laceration. Initially, an inflammatory papule or nodule forms which subsequently ulcerates. Usually the arm is affected, but the initial lesion may occur on the face, neck, or trunk. If no treatment is instituted the disease becomes chronic, and a chain of lymphatic nodules develops, which usually ulcerate after a period of time. The primary lesion may or may not heal; untreated the disease may last for years.

Disseminated or hematogenous sporotrichosis represents the second clinical type which may occur. It is rare and manifested by disseminated ulcerated nodules that may occur anywhere on the skin, mucous membranes, or viscera. Bones and joints may also be involved.

The clinical picture of the localized lymphatic variety occurring on the arm is classic (Figure) and can be diagnosed with considerable confidence. Tularemia, syphilis, glanders, anthrax, pyogenic lesions, cutaneous and lymphatic



Figure

tuberculosis may present a picture similar to the disseminated form of sporotrichosis. Recently, atypical mycobacterium infection has been shown to produce a sporotrichosis-like picture. A number of the fungi, including coccidioidomycosis, blastomycosis, histoplasmosis, and American leishmaniasis, may also produce a clinical complex identical with sporotrichosis.

Laboratory diagnosis is made by observing the characteristic microscopic picture of the fungus on artificial media. The fungus, *Sporotrichum schenckii,* is dimorphic, growing on artificial media at room temperature as a mycelial mat and, at incubator temperature, as a yeast-like budding organism. Animal inoculation may be helpful, but diagnosis can usually be made from culture.

The treatment of choice for sporotrichosis is a saturated aqueous solution of potassium iodide administered in the form of drops in water or milk. The beginning dose should be 15 drops three times daily with an increase to 30 to 40 drops three times daily. This dose should be maintained from four to six weeks after the eruption has healed.

Samuel F. Bean M.D.
Minneapolis, Minnesota

It's the Law

New Film on Medical Witnesses Available

A new film to show physicians what will be expected of them if they are called upon to be medical witnesses in personal injury litigations is available upon request. This film stresses the desirability for both the physician and the attorney for pretrial preparation and demonstrates how problems can be avoided. This film is well suited for presentation on medical school programs, hospital staff programs or at medical society meetings.

The film is 16 mm. colored sound movie and runs 30 minutes. It was produced in 1969 and is available through William S. Merrill Company, the American Medical Association or the American Bar Association.

Theodore A. Peterson, M.D.
Minneapolis, Minnesota

The Citation, Vol. 20, No. 4, December 1, 1969.

The maid was ill. Her mistress sent for the M.D., who, upon arriving, asked the lady to leave the room during his examination.

When the maid was alone with the physician she confessed, "Doctor, I'm not really ill. She owes me six weeks' salary and I'm not getting out of bed until she pays me."

"She owes me for the last ten visits I've made here," said the physician. "Move over."*

*Dr. Francis Leo Golden: Jest What the Doctor Ordered.

Democracy

". . . If you can't have an unpopular idea in a free society, and still survive—and be permitted to state that idea—then there is no democracy."—Hubert H. Humphrey

Schering

After only one year:

Administered to more people than live in Duluth, Winona, and Bloomington.*



Injectable
Garamycin®
brand of gentamicin sulfate injection

*An estimated 208,000 patients have received GARAMYCIN Injectable to date. The combined population of Duluth, Winona, and Bloomington is 205,500. (Estimated 1969 figures from The New York Times Encyclopedic Almanac 1970.)

See Clinical Considerations section on last page...

Mounting acceptance in the hospital...

Proven clinical effectiveness



Respiratory Infections

Outstanding results in serious gram-negative respiratory infections[1,2]

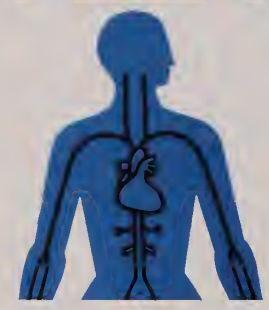
GARAMYCIN Injectable may prove successful where other antibiotics have failed.



Urinary Tract Infections

Strikingly effective in selected urinary tract infections[3]

With relatively low intramuscular doses, the promptly attained levels of GARAMYCIN achieved in the urine are considerably higher than the concentrations required for effectiveness against virtually all susceptible gram-negative pathogens. (Appropriate precautions are indicated in patients with impaired renal function; consult Package Insert for full details.)



Septicemia

May be lifesaving[4-6]

Numerous investigators have drawn attention to the value of GARAMYCIN Injectable in the treatment of gram-negative septicemias, often complicated by shock. Many hospital strains of *Serratia* are susceptible.[6]



Wounds and Burns

Response may be dramatic in wounds and burns complicated by sepsis[7]

The established efficacy of GARAMYCIN Injectable against *Pseudomonas*—as well as most other gram-negative pathogens—makes it an especially useful agent in the treatment of infected wounds and burns.

Important Precautionary Note Patients receiving treatment with GARAMYCIN Injectable (gentamicin sulfate injection) should be under close clinical observation because of the toxicity associated with the use of the drug. Ototoxicity, vestibular and auditory, can occur in patients, primarily those with preexisting renal damage, treated with GARAMYCIN Injectable for longer periods or with higher doses than recommended.

GARAMYCIN Injectable is potentially nephrotoxic, and this should be kept in mind when it is used in patients with preexisting renal damage.

This drug should be limited to the treatment of serious infections caused by susceptible gram-negative bacteria, with due regard for relative antibiotic toxicity. (See Clinical Considerations section.)

Mounting evidence in the laboratory...

Schering

Over 95% gram-negative pathogens sensitive.*

No other antibiotic performed comparably *in vitro* against gram-negative pathogens.
In a nationwide culture audit of antibiotic sensitivity patterns, sensitivity reports from 106 hospitals, geographically representative by census tract and of varying sizes, were analyzed. During the three-month period, ***every*** gram-negative culture slip from ***every*** hospital was surveyed. The total number of cultures involved in the audit was 97,091. The total number of sensitivity determinations was 643,503.

Pathogens	Percentage of sensitive strains Number of strains tested Antibiotics*							
	Garamycin	Kanamycin	Cephalothin	Cephaloridine	Ampicillin	Colistimethate	Chloramphenicol	Tetracycline
Klebsiella pneumoniae	99.5% 962	84.7% 992	86.2% 995	76.1% 67	32.7% 1,020	96.3% 640	82.9% 1,028	77.1% 1,026
Aerobacter aerogenes	95.9% 2,739	86.1% 2,818	53.5% 2,985	58.8% 1,514	22.7% 3,066	88.6% 2,603	85.8% 3,071	67.8% 2,981
Klebsiella aerobacter group	98.8% 566	83.9% 547	66.1% 522	60.5% 276	28.0% 553	89.5% 560	86.2% 587	62.8% 433
Klebsiella, all others	92.7% 2,944	83.3% 3,186	77.4% 2,976	67.5% 627	13.5% 2,883	95.0% 2,105	81.6% 3,212	70.6% 3,063
Pseudomonas aeruginosa	91.6% 4,528	29.8% 4,460	6.6% 4,418	6.6% 1,279	6.0% 4,360	91.3% 3,852	26.9% 4,608	26.4% 4,404
Proteus, indole-positive	91.8% 1,031	85.8% 1,062	39.9% 981	54.1% 364	40.2% 1,042	10.3% 758	76.1% 1,096	42.1% 1,051
Proteus mirabilis, indole-negative	94.9% 3,272	90.1% 3,378	83.1% 3,290	77.5% 975	78.0% 3,274	8.8% 2,634	85.9% 3,469	26.8% 3,278
Proteus, unspecified	96.2% 1,335	85.8% 1,371	71.7% 1,434	70.0% 647	64.7% 1,435	11.2% 1,233	76.0% 1,421	22.4% 1,298
Escherichia coli and all other Escherichias	96.4% 12,557	91.4% 12,818	87.8% 12,686	88.8% 4,251	74.6% 12,899	95.4% 10,623	94.1% 13,086	70.0% 12,559
Paracolobactrum, all	93.4% 303	88.9% 325	62.0% 305	74.2% 62	43.8% 340	80.9% 215	87.1% 350	72.6% 340
Coliform bacteria	99.0% 593	91.2% 649	81.5% 637	66.7% 21	52.7% 624	95.6% 607	91.6% 678	76.1% 637
Totals	95.1% 30,830	80.5% 31,606	65.3% 31,229	68.1% 10,083	50.3% 31,496	75.8% 25,829	79.7% 32,606	56.5% 31,070
Gram-positive (included for consistency with Package Insert, not an approved indication)								
Staph—*S. aureus, coagulase-positive*	97.4% 1,548	88.8% 1,458	97.7% 2,050	98.7% 636	61.1% 1,559	20.4% 628	94.4% 2,123	83.7% 1,966
Staph—*S. aureus, unspecified*	99.3% 993	92.8% 902	98.1% 1,289	95.3% 213	45.8% 1,153	29.3% 116	96.4% 1,427	82.3% 1,360

*Adapted from a three-month, nationwide hospital audit by R. A. Gosselin and Co., Inc., Dedham, Massachusetts (mid-May to mid-August, 1969).[8]
Antibiotics with significant gram-negative spectra are included. Organisms are listed as reported by laboratory.
Sensitivity testing was done by the disc method, a generally reliable test in the hospital setting. It should be noted, however, that the results with GARAMYCIN were somewhat higher than the results reported where the tube dilution technique was used. (See Clinical Considerations section which follows.) The concentration of the GARAMYCIN disc was 10 mcg.
Whereas standard testing methods were used by all hospitals, it is acknowledged that in a survey of this kind considerations such as differences in methodology are possible sources of error. The comparative percentage-sensitivity results derived from a survey of this kind are, therefore, not absolute. One should keep in mind also that the proper selection of an antibiotic is based not only on susceptibility testing but on relative toxicity and other clinical considerations as well.
It is felt, nonetheless, that the broad scope of the survey and the extreme care in data collection and tabulation permit a conclusion that the results are *generally* representative of current nationwide antibiotic sensitivity patterns.

Injectable Garamycin®
brand of gentamicin sulfate injection

See Clinical Considerations section on last page...

Injectable Garamycin®

brand of gentamicin sulfate injection

ADULT DOSAGE GUIDELINES

See definitive prescribing information in Package Insert.

Patients with Normal Renal Function

Total Daily Dose (administered in two, three, or four divided doses)			
	Less Severe	Resistant/ Moderately Severe	Serious/Life-Threatening
Urinary Tract Infections (due to susceptible strains of gram-negative bacteria)†	0.8-1.2 mg./kg. for 7-10 days	Larger doses or additional antibacterial therapy should be considered in severe urinary tract infections or in resistant cases involving the renal parenchyma or anatomic anomaly.	up to 5 mg./kg.
Other Infections including bacteremia, infected surgical wounds, severe soft tissue infections, and respiratory tract infections (due to susceptible strains of gram-negative bacteria)	3 mg./kg. for 7-10 days		

†Alkalinization of the urine may be a useful therapeutic adjunct.

Patients with Impaired Renal Function

To minimize the risk of ototoxicity in patients with impaired kidney function, only the first dose should be that normally recommended. Each subsequent dose should be half or less of that recommended for patients with normal renal function, depending upon the degree of renal impairment.

In patients with renal failure who are undergoing 14-hour hemodialysis twice weekly, administration of 1 mg./kg. GARAMYCIN Injectable at the end of each dialysis period has been suggested.

Clinical Considerations

Indications: GARAMYCIN Injectable is clinically effective in infections due to susceptible strains of gram-negative bacteria, including *Pseudomonas aeruginosa,* and species of indole-positive and indole-negative *Proteus, Escherichia coli,* and *Klebsiella-Aerobacter.* Bacteriologic studies should be conducted to identify the causative organism and to determine its sensitivity to gentamicin sulfate. Sensitivity discs of the drug are available for this purpose. If the susceptibility tests indicate that the causative organism is resistant to gentamicin sulfate, other appropriate antibiotic therapy should be instituted.

IN VITRO INHIBITION OF CLINICALLY IMPORTANT BACTERIA BY GENTAMICIN SULFATE (TUBE DILUTION STUDIES)

BACTERIA	No. of Strains Tested	No. of Strains (%) Inhibited by: 4 mcg./cc. or less		8 mcg./cc. or less*		No. of *In Vitro* Studies
Staphylococcus aureus	1,210	1,200	(99%)	1,206	(99%)	11
Pseudomonas aeruginosa	885	771	(87%)	828	(93%)	16
Escherichia coli	836	736	(88%)	779	(93%)	11
Indole-positive and indole-negative *Proteus* species	477	210	(44%)	358	(75%)	12
Klebsiella-Aerobacter species	292	205	(70%)	231	(79%)	10

*Number of strains (%) of gram-negative bacteria inhibited by 10 mcg./cc. or less are as follows: *Pseudomonas aeruginosa,* 828 (93%); *Escherichia coli,* 792 (95%); *Proteus* species, 393 (82%); *Klebsiella-Aerobacter* species, 284 (97%). From same studies as above.
Source: Package Insert

This drug should be limited to the treatment of serious infections caused by gram-negative bacteria, particularly *Pseudomonas aeruginosa, Proteus* and other susceptible organisms, with due regard for relative antibiotic toxicity. Therefore, the drug should be considered for use against gram-negative: 1. Bacteremia; 2. Infected surgical wounds; 3. Severe soft tissue infections, including burns complicated by sepsis; 4. Respiratory tract infections; and 5. Selected cases of urinary tract infection.

Contraindications: GARAMYCIN Injectable is contraindicated in individuals with a history of hypersensitivity or toxic reactions to gentamicin.

Warnings: Patients receiving treatment with GARAMYCIN should be under close clinical observation because of the toxicity associated with the use of this drug. Ototoxicity, vestibular and auditory, can occur in patients, primarily those wi pre-existing renal damage, treated with GARAMYCIN Injectabl usually for longer periods or with higher doses than recommende

GARAMYCIN Injectable is potentially nephrotoxic, and th should be kept in mind when it is used in patients with pre-existin renal impairment. Kidney function diminished by infection of th upper urinary tract may, however, improve during effective trea ment with GARAMYCIN Injectable.

Concurrent administration of potentially ototoxic drugs such streptomycin and kanamycin or of potentially nephrotoxic dru such as polymyxin, colistin, and kanamycin with gentamicin sulfa has not been shown to afford any clinical advantages and, moreov may result in additive toxicity. Monitoring of vestibular, cochlea and renal function will provide guidance for therapy in such case

Precautions: In patients with impaired renal function in who serious infection develops, serum concentrations of the drug ma rise, with consequently increased risk of ototoxicity. In these p tients or in those in whom recommended dosage or duration therapy must be exceeded as a life-saving measure, routine studi of kidney function should be performed when possible. These m be supplemented by evaluation of the vestibular and auditory fun tion and measurement of serum concentration of the drug whe feasible. Serum concentrations of gentamicin should be maintain below the range of 10-12 mcg./ml. to reduce risk of ototoxicity.

Ordinarily, treatment should not be given for more than 7 to days or be repeated unless required for serious infection not r sponsive to other agents.

As with other antibiotics, treatment with GARAMYCIN Injectab may occasionally result in overgrowth of nonsensitive organisms. superinfection occurs, appropriate therapy is indicated.

Safety for use in pregnancy or the potential for fetal ototoxicity nephrotoxicity have not been established. Studies in pregnant an mals have not revealed teratogenic or ototoxic effects in the fetu GARAMYCIN Injectable should not be used in pregnant patients in women of childbearing age unless its use is deemed advisab by the physician.

Adverse Reactions: The overall incidence of ototoxicity considere related to treatment with GARAMYCIN Injectable was 2.8 per ce (16 of 565 patients). Contributory factors (two or more factors we relevant to most patients) were as follows: 10 had azotemia, received a total of 1 gram or more of the drug, 7 had recently r ceived other potentially ototoxic antibiotics (streptomycin or kan mycin), and 5 were over 60 years of age. Six also had decreas high-tone hearing acuity, which returned to or toward normal the 4 patients retested.

Analysis of BUN data indicated that 4 (2%) of 172 patients show increases in BUN that were probably related to treatment wi GARAMYCIN Injectable. Of 20 increases probably or possibly relat to treatment, 7 were reversible, 9 occurred in terminal patients, a 4 had no follow-up.

Other adverse reactions associated with treatment were one instan each of urticaria, decreased hematocrit, and reversible depressi of granulocytes with normal bone marrow. Other rarely report and possibly treatment-related adverse reactions were anemia, i creased reticulocyte count, rash, purpura, drug fever, hypotensio convulsions, twitching, salivation, nausea, vomiting, increased tra aminase activity (SGOT or SGPT), increased serum bilirubin, c creased serum calcium, and joint pain.

Packaging: GARAMYCIN Injectable, 40 mg./cc., 2-cc. multiple-d vials, for intramuscular administration.

References: (1) Brayton, R. G., and Louria, D. B.: Gentamicin gram-negative urinary and pulmonary infections, Arch. Int. M *114*:205, 1964.* (2) Louria, D. B.; Young, L.; Armstrong, D., a Smith, J. K.: Gentamicin in the treatment of pulmonary infectio J. Infect. Dis. *119*:483, 1969. (3) Cox, C. E.: Gentamicin, a n aminoglycoside antibiotic: Clinical and laboratory studies in urina tract infections, J. Infect. Dis. *119*:486, 1969. (4) Groll, E.: Clini experience with gentamicin, data from 12 German clinics, in G tamicin: First International Symposium, Paris, January 19 Lucerne, Essex Chemie AG, pp. 121-128.* (5) Jackson, G. G.: Labo tory and clinical investigation of gentamicin, *ibid.*, pp. 62-74. Medeiros, A. E.: Discussion, J. Infect. Dis. *119*:533, 1969. (7) Polk, Discussion, J. Infect. Dis. *119*:529, 1969. (8) Three-month, nationwi hospital audit by R. A. Gosselin and Co., Inc., Dedham, Massachuse (mid-May to mid-August, 1969).

*Dosage in this investigational study was less than now recommend in Package Insert.

For more complete prescribing details, consult package insert Physicians' Desk Reference. Schering literature is also availa from your Schering Representative or Medical Services Departme Schering Corporation, Union, New Jersey 07083.

AHFS CATEGORY 8:12.28 5-0

Otolaryngology Clinics

Meniere's Disease*

Natural History

Meniere's disease is episodic, with attacks of severe, disabling symptoms followed by remissions in which the patient feels perfectly well. The dramatic feature of the attacks is an episode of acute, severe, whirling vertigo in which the environment spins around the stricken individual or in which he feels that he is being pushed in one direction or another. If recumbent, he feels that his bed may fall away from him. This vertigo is so severe that it prevents walking. It is aggravated by any motion, so that the individual tends to lie in bed fixed in one position. The attack, which persists for a period of a few minutes to several hours, is accompanied by profuse perspiration, nausea, and often vomiting. Following subsidence of the acute symptoms, the individual feels unsteady and uneasy for a period of a few hours to two or three days. During this episode there is a sensation of dysfunction in an ear: a sense of fullness or pressure, of tinnitus which characteristically is of a buzzing or roaring type, and of disturbed hearing. The hearing disorder consists of elevation of threshold, especially for low tones, and of distortions, both of loudness, which results in a sense of discomfort or pain from loud sounds, and of pitch, which results in disharmony. The distortion tends to make music and voices unpleasant and causes a loss of ability to understand speech which is out of proportion to the pure-tone threshold. In the characteristic attack the pressure and cochlear symptoms precede the onset of vertigo and warn of an impending attack. The symptoms ascend to a peak during the active vertigo and then gradually recede.

The first episode usually takes the patient by complete surprise. Thus warned, he is apt to be very apprehensive of subsequent attacks. Recurrences may come at intervals varying from a few days to several years and tend to come in groups. The usual textbook description indicates complete remission of all symptoms during the early stages of the disease. These descriptions usually suggest that, with repeated attacks, residual tinnitus and hearing deficit are apparent during remissions, that the hearing loss is progressive and that, as the loss becomes severe, the episodes of vertigo lessen or cease, leaving a deafened patient with tinnitus but without fear of recurrent vertigo.

The condition is said to be bilateral in 10 to 20% of cases. Some descriptions imply that in bilateral disease the two ears become involved within a short interval of time.

This description of a stylized pattern of progress for Meniere's disease fits a few cases and the pattern might be taken as the mean of a curve in which the many variants are described. The variations of the pattern are so great and so frequent that it seems impractical to attempt to set any single pattern of symptoms or any single course of progress and to say that this represents an adequate description of Meniere's disease. The following case records illustrate some of the many variations in the symptom pattern and course presented by this disorder.

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*Modified and reprinted with permission of the publisher, W. B. Saunders Company, from Otolaryngologic Clinics of North America, October, 1968, pp. 423-432.

Illustrative Cases

Case 1

In 1933 at age 31 a man noted the onset of tinnitus in his right ear. This came at intervals of two to eight weeks and persisted for two to 20 days, varying in pitch and in intensity. Hearing in the right ear was reduced during the episodes and normal during remissions. During an episode in 1935 the tinnitus increased in intensity and was followed by vertigo, nausea, vomiting, and sweating. Subsequent attacks followed a similar pattern, lasting one to three hours, a pattern which persisted until 1952. By this time he had lost all useful hearing in the right ear. The tinnitus persisted. He had no further vertigo.

This patient demonstrates gradual onset of symptoms. Vertigo appeared late in the course and disappeared when hearing loss became severe.

Case 2

In 1930 at age 47 a woman noted onset of tinnitus in her left ear. In 1932 she experienced dizziness. In 1937 she described a continuous roaring in each ear, loss of hearing, and episodes of rotatory vertigo. By 1942 these increased to a frequency of once a week but were absent during 1944. The episodes persisted at a frequency of one to two per year until 1959 when she was 75 years of age.

This case demonstrates slow onset of symptoms with increasing frequency and severity of the episode over a period of years. The frequency decreased in late years of the disorder.

Case 3

In 1957 at age 50 a man suffered a sudden severe episode of vertigo with associated nausea and vomiting, high-pitched tinnitus in the left ear, and reduced hearing. Similar episodes were repeated once a week, each episode heralded by profuse perspiration and lasting two hours. He was unable to walk during the episode. He was free of vertigo from 1958 to 1961. Constant hearing loss persisted; tinnitus fluctuated in degree. From 1961 to 1967 he experienced one episode per year, but these were not disabling in severity.

This case demonstrates an abrupt onset of symptoms with decreasing frequency and severity of the episodic vertigo.

Case 4

A 58-year-old woman had experienced episodes of vertigo with transient reduction of hearing in the left ear annually for 10 years. Tests revealed normal hearing and hypoactive response to caloric stimulation in her left ear. Two weeks later she experienced an episode of vertigo, nausea, and vomiting associated with tinnitus, fullness, and hearing loss in the left ear. Three days later the tests showed low-tone hearing loss and absence response to caloric stimulation on the left. After another 10 days, findings returned to the pre-attack level.

This case illustrates absence of permanent change in hearing over a 10-year period.

Case 5

A man experienced the onset of recurring episodes of imbalance in 1935 at age 33. These recurred infrequently until 1954, after which they increased in frequency. He did not experience nausea and was able to walk although he staggered during attacks. In 1951 he noted the onset of hearing loss in the right ear which was subtly progressive without fluctuation, but he was not aware of fullness or tinnitus in the ear. Because of his uncertainty he feared open places. Examination gave normal results except for sensorineural hearing loss in the right ear with special features suggesting Meniere's disease. At operation for destruction of the labyrinth in 1967, findings suggested chronic dilatation of the endolymphatic system. His symptoms were relieved.

This case illustrates imbalance rather than vertigo.

Case 6

A university professor who was unusually accurate in observing and reporting his symptoms, in October 1960 at age 63, noted onset of hearing loss in the left ear characterized by distortions of pitch and loudness. He did not experience vertigo or tinnitus. After fluctuating, the hearing loss became constant in February 1961. Hearing tests revealed loss of hearing in the right ear in May 1961 with recovery two months later. In October 1961 the symptoms recurred and remained for two years. In July 1966 he experienced tinnitus in both ears with loss and distor-

tion of hearing in the right ear. Tests revealed severe loss of hearing in the right ear with normal hearing in the left. Two weeks later, hearing in the right ear had returned to its previous level.

This case illustrates bilateral Meniere's disease without vestibular symptoms and with a five-year interval between onset in the first and second ear.

Case 7

At age 41 a woman noted the onset of episodic vertigo associated with nausea and vomiting, hearing loss, tinnitus, and fullness in both ears. Vertigo was aggravated by movement and she was unable to walk without support. Tinnitus and fullness persisted until she was examined five years later. Her hearing was reduced only at the time of attack.

This case demonstrates bilateral symptoms with simultaneous onset.

Case 8

In 1947 at age 40 a woman noted gradual onset of hearing loss in the left ear; the hearing loss and accompanying tinnitus were constant. She experienced a single episode of vertigo. Twelve years later she noted the onset of tinnitus in the right ear accompanied by a sensation of fullness in the head and four months later by a "severe explosion" of vertigo. In 1960 she suffered numerous episodes of the Lermoyez type in which hearing loss and tinnitus in the right ear built up gradually over a period of five hours to two days. At the peak a sudden episode of vertigo disabled her for four to six hours. With subsidence of vertigo, hearing returned to the right ear. During this period the hearing loss and tinnitus in the left ear remained constant. In 1967 she experienced an attack of the utricular-crisis type. In this episode she was struck without warning with very sudden severe vertigo; she was totally unable to maintain her posture and fell, cutting her head and breaking her ankle. She did not lose consciousness and felt free of vertigo after a few seconds.

This case illustrates bilateral involvement with a 12-year interval between attacks and marked variation in the character of the episodes, including episodes characteristic of both the Lermoyez and utricular-crisis variant of the symptom complex.

Case 9

A girl examined in 1923, at age four and a half years, had hearing loss of undetermined type. In 1943 she noted the onset of transient bilateral tinnitus and experienced a single attack of vertigo with nausea and vomiting. From 1944 to 1946, episodes characteristic of Meniere's disease occurred at intervals of one week to one month. Episodes were infrequent from 1948 to 1950 and absent until 1958, when she experienced six severe episodes within one month.

This case illustrates long remissions and a cluster grouping of attacks.

Case 10

In 1947 at age 48 a woman experienced several episodes of vertigo and nausea followed by unsteadiness over a period of one month. She was then free of symptoms until July 1967 when she experienced a sense of fullness in the right ear while sitting quietly and was struck by sudden severe vertigo with accompanying nausea and vomiting. She required help to get to a couch. She remained in bed for four hours, after which she felt unsteady for one week.

This history demonstrates a 20-year interval between first and second episodes.

Summary

Ten cases are presented to demonstrate several contrasts in the pattern of symptoms accompanying endolymphatic hydrops (Meniere's disease).

These variations in pattern demonstrate the need for an open mind, for repeated observations including tests of function and, in some instances, for long observation in making the diagnosis of endolymphatic hydrops.

Kinsey M. Simonton, M.D.*
Rochester, Minnesota

*Mayo Clinic and Mayo Foundation: Section of Otolaryngology and Rhinology.

Can one desire too much of a good thing?—Cervantes

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Case Report

Systemic Lupus Erythematosus Presenting as Regional Ileitis

REX B. SHAFER, M.D.*
DANIEL H. GREGORY, M.D.*
Minneapolis, Minnesota

When a patient with known systemic lupus erythematosus develops an acute surgical abdomen, it is usually the result of vasculitis‡ of the bowel wall. If this occurs in a relatively young individual, the more frequent etiologies are often overlooked. The following case illustrates that the acute abdominal process need not be related to the primary disease; acute appendicitis, regional ileitis, diverticulitis, or peritonitis still need to be considered.

Case Report

A 35-year-old white male granite worker was referred to the Minneapolis Veterans Hospital for evaluation of nephritis and pleurisy.

Past History

Three months prior to admission he had been evaluated for a left pleuritic chest pain with associated hematuria and proteinuria. He also complained of migratory joint pains, anorexia with a 25-pound weight loss and easy fatiguability. There was no evidence of skin rash, alopecia or central nervous system involvement. A diagnosis of systemic lupus erythematosus was established. At that time he had two positive lupus erythematosus clot tests, a reactive latex fixation, and a false positive venereal disease reaction. An intravenous pyelogram showed poor bilateral renal function. An upper gastrointestinal series with small-bowel follow-through was negative. There had been marked improvement following oral corticosteroid therapy (5 mgm prednisone® four times daily).

Admission Findings and Procedure

On admission to this hospital, the patient complained of persistent epigastric pain, with a recurrent urge to defecate. On the second day he developed nausea with vomiting, a temperature of 100.4° and persistent lower abdominal pain. Guarding and rebound tenderness were present in both lower quadrants on the following day. A low-grade temperature and slight leucocytosis persisted. X-rays of the abdomen showed a small bowel loop containing air-fluid levels suggestive of partial obstruction. An operation was performed based on the clinical impression of acute appendicitis with localized ileus.

Pathology

The surgical findings showed a normal appendix and an area of thickened, edematous, reddish purple, distal ileum with marked narrowing of the lumen. The adjacent mesenteric lymph nodes were enlarged. A "skip lesion" involving an additional 15 cm of small bowel was located approximately 12 inches proximal to this lesion; the remainder of the small bowel appeared normal. The involved segment of bowel was not excised. Regional ileitis was the most compatible clinical and surgical diagnosis. Although the abdominal symptoms subsided, hematuria and proteinuria persisted. One week after surgery an upper gastrointestinal series with small-bowel follow-through demonstrated an area of persistent narrowing in the terminal ileum with apparent rigidity, and an irregular mucosal pattern again consistent with regional ileitis (Figure).

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‡See Test Your Word Score, page 753.
Address requests for reprints to: Rex B. Shafer, M.D., Minneapolis Veterans Hospital, Minneapolis, Minnesota 55417.

Therapy

The postoperative course was uncomplicated and the patient was continued on corticosteroid therapy, now increased to prednisone, 90 mgm daily. He remained in the hospital because of continuing deterioration of renal function. Steroid medication was increased to 100 mgm prednisone daily because of a falling hemoglobin and a progressive rise in blood urea nitrogen and serum creatinine. In spite of this therapy the patient became progressively azotemic and hyperkalemic. Three months after admission, he was started on peritoneal dialysis with an initial satisfactory response, but later developed an acute hypertensive episode with congestive heart failure. Intractable pulmonary edema resulted in his death. At postmortem, typical findings of systemic lupus erythematosus were found in the kidneys. Patchy areas of dark pigmentation were seen in the small intestine, apparently related to terminal superficial bleeding. There were superficial erosions with ulceration seen in the terminal ileum associated with submucosal scarring and involving a "skip lesion," 15 cm proximally. Most significant was the lack of specific vascular or acute inflammatory disease, either on the gross specimens or on microscopic histology. The previously enlarged lymph nodes were now essentially normal; no involvement was observed microscopically.



Figure—Regional ileitis. Arrow indicates area of involved ileum.

Comments

In spite of the many gastrointestinal manifestations of systemic lupus erythematosus, there have been relatively few instances of colitis or enteric processes described, presenting as an acute surgical abdomen. Pollak et al.,[1] in 1958, described 14 cases of systemic lupus erythematosus simulating an acute surgical condition of the abdomen. Ten of the 14 patients described were demonstrated to have gastrointestinal disease as a result of vascular lesions of the submucosal or subserosal layers of the bowel wall. In four patients a clinical diagnosis of pancreatitis was made. All of these patients had proven systemic lupus erythematosus with symptoms severe enough to warrant surgical consultation. In four the predominant clinical picture was that of pancreatitis. Ten had lupus peritonitis and four of these had an abdominal operation. Vascular lesions of the bowel wall were the predominant findings on the surgical pathological specimens.

Brown et al.,[2] in 1956, reviewing the gastrointestinal manifestations of systemic lupus erythematosus in 87 patients, found only seven with severe gastrointestinal symptoms. Five of these seven had symptoms suggesting an acute abdominal obstruction; two were found to have ulcerative colitis. In this review no mention was made of regional ileitis. In fact, except for a single case report by Dubnow et al.[3] in 1966 of lupus erythematosus presenting as an acute abdomen, there has been no previous mention of the coexistence of this disease with regional ileitis. They described a young man with an acute abdomen who on exploration was felt to have regional ileitis based on the histological appearance of resected bowel and whose clinical course was compatible with systemic lupus erythematosus. No serological evidence was obtained; the diagnosis was based on the presence of circulating cryoglobulins, in addition to positive serological reaction for syphilis. Vasculitis was not found in the resected bowel.

An acute surgical abdomen in a young patient with proven systemic lupus erythematosus presents a diagnostic dilemma. Gastrointestinal manifestations in the form of intestinal infarction, hemorrhage or perforation have been described, secondary to a diffuse inflammatory vasculitis.[4] On the other hand, diagnostic possibilities in any young patient with an acute abdomen still include appendicitis, hemorrhagic diverticulitis, perforated viscus, or peritonitis. For this reason it is not surprising that such a patient as the one described here would undergo an exploratory laparotomy. The clinical signs and symptoms in this particular case strongly suggested acute appendicitis; but at laparotomy the observed lesion was most compatible with regional ileitis. Failure to demonstrate the specific pathology of regional ileitis at postmortem suggests improvement in the bowel mucosa from prolonged steroid therapy.

Summary

The history of a 35-year-old man with proven systemic lupus erythematosus presenting with an acute abdomen is described. The etiology of the acute abdominal process was considered to be appendicitis but on surgical exploration was found to be most compatible with regional ileitis. Later, at postmortem, the specific pathologic lesions for regional ileitis were not present, suggesting possible modification from prolonged steroid therapy.

Gastrointestinal manifestations are not uncommon in systemic lupus erythematosus, although an acute surgical abdominal process is relatively rare. From

a review of the literature there appears to have been only a single previous case suggesting the coexistence of these two diseases. From the information available it is not possible to suggest a common etiology or causative relationship between these two entities.

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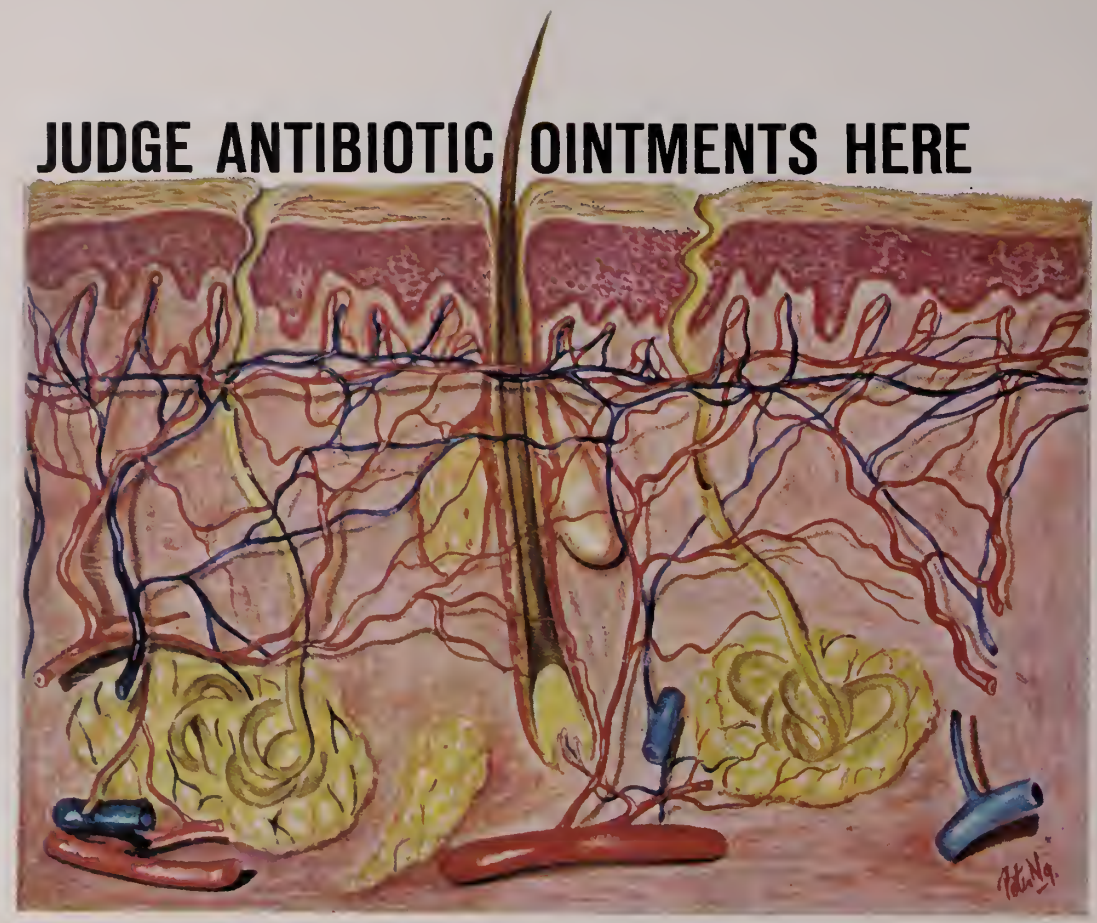
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(Continued to page 804)

Neurological Grand Rounds

Immunologic Aspects of Multiple Sclerosis

KHURSHED ANSARI, M.D.*

THERE ARE TWO basic assumptions which are relevant to immunologic considerations in multiple sclerosis: (A) Antibody forming system and (B) Autosensitization.

Immunologic Considerations

Antibody Forming System

The brain is an immunologically privileged organ. A long time ago it was shown that after intracerebral injection of polio virus in monkeys, little or no antibodies could be detected in serum.[1] However, large concentrations of antibodies could be demonstrated in the anterior horns of the spinal cord. This would make one suspect that because of the blood brain barrier and absence of lymphatics in the brain, the central nervous system may have its own unique and perhaps unconventional antibody-forming system. Detection of new immunoglobulins in cerebrospinal fluid and brain substance by Roboz-Einstein[2] and MacPherson[3] would lend support to this idea, as these globulins cannot be detected in serum.

Autosensitization

The second assumption concerns autosensitization. It is an interesting one. For autosensitization to occur, a break in immunologic self-recognition is essential. For example, it has been shown by Salvin that guinea pigs can be made to produce antibodies against their own albumin, if the albumin was first mildly denatured by heating at 60°C for one-half hour.[4] Thus, before an organism can make antibodies against its own myelin, the myelin would have to

*Veterans Administration Hospital, Minneapolis, Minnesota.

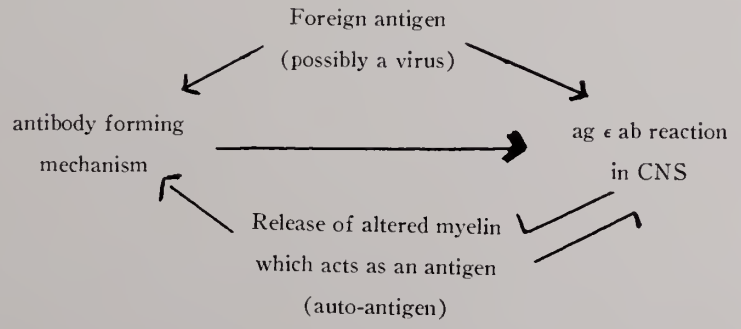


Fig. 1—A foreign antigen, possibly a virus, stimulates the antibody-forming mechanism and also causes an abnormal reaction in the central nervous system. Altered myelin is released and acts as an auto-antigen causing further stimulation of antibody response and further damage to the central nervous system by autosensitization.

be altered somehow—for example, by infection or by a chemical reconfiguration (Figure 1). This would make one look for immunologic sequelae to multiple sclerosis rather than an immunologic etiology of the disease. A glance at currently available literature indicates a plethora of information regarding these sequelae.

The immunological sequelae of multiple sclerosis can be divided in three groups: (1) An impairment in antibody formation against administered antigens, (2) Abnormal antibody formation against "Unrelated" antigens and (3) Formation of antibodies against myelin, its precursors, degradation products or the basic protein of central nervous system.

This central nervous system basic protein is called encephalitogenic factor or experimental allergic encephalitic antigen. A number of workers in this country and abroad have utilized this compound as an antigen and have tested multiple sclerosis sera and spinal fluids against it. Although there seems to be some difference in the compounds used by the two more active groups, viz., Marian Kies and co-workers in this country and Fields and Caspary from England; basically, it is a product of chemical extraction from white matter having a molecular weight of about 20,000 and an ultracentrifuge mobility of 1 Svedburg Unit. A polypetide of moleucular weight 5-6000 derived from the protein is also active.[9]

Impaired Antibody Formation against Administered Antigens

Southam and co-workers showed rather inconclusively that terminal patients with cancer do not produce antibodies as well as healthy individuals of the same age.[5] Few studies have attempted to test this situation in multiple sclerosis patients. The work of Foley and Sibley[6] from Cleveland stands out. These workers immunized controls and multiple sclerosis patients with influenza, measles and polio vaccines and tested the sera for antibodies one month later. A comparison of pre- and post-immunization titers in patients and controls failed to show any significant impairment of immunologic capacity in the multiple sclerosis patients in various stages. The number of patients tested, however, was rather small, as the workers were concerned about vaccination producing an exacerbation in disease.

Antibodies against "Unrelated" Antigens

The word "unrelated" is in quotes because there may actually be a close association between some of the antigens, e.g., measles virus and the subacute sclerosing leukoencephalitic agent of Dawson.

Adams and Imagawa[7] and other workers have shown that a certain proportion of multiple sclerosis patients have in their sera anti-measles antibodies in slightly excessive amounts compared to the controls. A still smaller proportion of patients demonstrate slight increase in the antibody titer to measles in cerebrospinal fluid.

As some Swedish workers had reported high anti-streptolysin-O titers in multiple sclerosis patients, Foley[6] also compared anti-streptolysin-O titer in multiple sclerosis and control patients; but his findings do not conform to those of the Swedish group. Also, there was no significant change in the titers of heterophile agglutinins. Should an infectious agent be involved in causing multiple sclerosis, screening patients for viral antibodies may offer significant clues.

Antibodies to Myelin

There are three convenient materials suitable for search for antibodies: serum, cerebrospinal fluid and lymphocytes in peripheral blood and cerebrospinal fluid.

Most of the work has been done with *serum.*[8,9] Precipitation in agar gel, complement fixation and tissue culture are the methods commonly employed. The last method using cultures of rat cerebellum and trigeminal ganglia introduced by Murray Bornstein,[10] although a bit complicated, affords an opportunity to visualize directly the destruction of myelin and glial cells. These workers have shown that a significant proportion of sera from multiple sclerosis patients when added to the culture causes swelling and then destruction of myelin sheath. Experimental allergic encephalitis sera have the same effect, and the presence of complement is essential for this reaction to occur. Although fraught with pitfalls, as are most biological systems, this avenue of research has attracted much attention and is being hotly pursued.

Cerebrospinal Fluid

Studies with *cerebrospinal fluid* are mainly directed toward finding new globulins, presumably antibodies. The most extensively utilized tool has been immunoelectrophoresis.[2,3,11] A number of workers have demonstrated IgG or 7s γ-globulin in cerebrospinal fluid. Tourtellotte and co-workers[12] have recently shown that the concentration of IgG may be 2.5 times greater in the developed plaques as well as in shadow-plaques in white matter of multiple

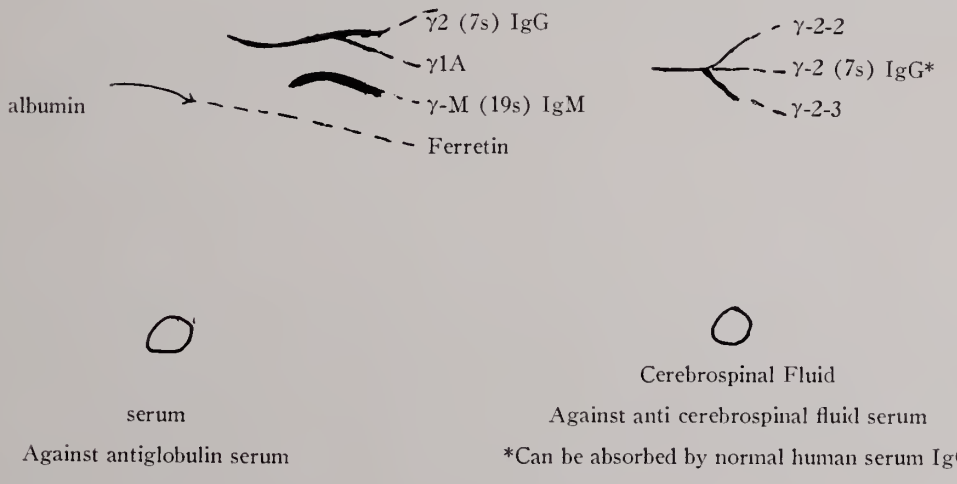


Figure 2

sclerosis brain. IgG is also increased in cerebrospinal fluid of the patients. It should be remembered, however, that IgG is ordinarily present in normal cerebrospinal fluid. Of more interest are the 7s globulins described independently by MacPherson[3] and Roboz-Einstein[2] that are not present in serum. These have been variously called γ-2-2, γ-2-3, and γ-c (Figure 2).

The virtually unlimited opportunities that need to be explored are imme-

diately obvious from reading the report of MacPherson[3] where, by using horse-serum instead of the previously employed rabbit-serum as developing agent, she has found yet another IgG in cerebrospinal fluid of multiple sclerosis patients.

It should be mentioned in passing that Kuwert and Pette[13] from Germany have reported lower levels of complement in cerebrospinal fluid of patients with acute multiple sclerosis when compared with normal cerebrospinal fluid.

Lymphocytes

Unfortunately *lymphocytes* have escaped the attention of most investigators working on multiple sclerosis. It was reported some time ago that if one took cultured peripheral blood lymphocytes from tuberculin-positive individuals and added tuberculin antigen to this culture, large numbers of these cells would be transformed into large lymphoblasts within three to five days (Figure 3). Similar studies were reported with lymphocytes in cases with dilantin sensitivity. This transformation, however, is not entirely specific, as phytohemagglutinin would produce similar transformation in even greater magnitude. Stimulated by these findings, Fowler and co-workers[14] tested the lymphocytes in peripheral blood of multiple sclerosis patients, using autologous* and homologous cerebrospinal fluid as antigen; and they found that transformation occurred in approximately 30% of cells. This transformation was noted to occur equally with multiple sclerosis and normal cerebrospinal fluid. This study is interesting also because here cerebrospinal fluid was used as antigen rather than an antibody-containing fluid. In a more recent study, Behan and co-workers[15] found that lymphocytes from two patients with primary demyelinating disease showed significant transformation when stimulated by a pure encephalitogenic basic protein derived from myelin.

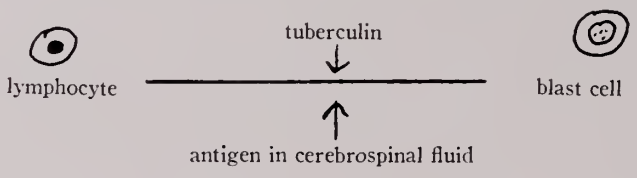


Figure 3

A look at the sensitivities of various methods for detecting antibodies (Table) would indicate that hemagglutination would be an ideal method. Unfortunately, tanned red blood cells are nonspecifically clumped by the basic protein antigen. Next in order would be passive cutaneous anaphylaxis.

TABLE

Test	Sensitivity[16] in microgram antibody Nitrogen
Precipitation	0.5–1
Agar gel diffusion	0.03–0.1
Complement fixation	0.12–0.4
Boyden's tanned red cell hemagglutination	0.003–0.006
Passive cutaneous anaphylaxis (Ovary)	0.003–0.01

*See Test Your Word Score, page 753.

A careful survey of the literature failed to reveal any evidence regarding the use of this method for detecting antibodies in cerebrospinal fluid. Passive cutaneous anaphylaxis is especially suited for 7s antibodies that are of special interest in multiple sclerosis. Also, the high degree of sensitivity of passive cutaneous anaphylaxis would be helpful because of the low protein content of cerebrospinal fluid.

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*John E. Eichenlaub, M.D.: The Minnesota Doctor's Home Treasury of Unusual Stress Easers, 1964.

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(Continued from page 798.)

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Maternal Mortality

Recent Trends in Infant and Maternal Health in Minnesota

A. B. ROSENFIELD, M.D.*, ROBERT W. HILLER, M.S.†,
HARRIET J. KELLY, Ph.D.‡

HEALTH IS MEASURED largely in terms of trends. While social and economic conditions, urban-rural distribution of the population, and other factors also affect mortality, changes in the number or rate of deaths, complications, injuries, or anomalies during a specific time interval serve to indicate community health problems, and more specifically to point out the problem of high-risk infants and mothers. What is the status of Minnesota? Is the health of mothers and infants improving, stationary, or regressing?

Birth and Fertility Rates

Provisional statistics from the Section of Vital Statistics, Minnesota Department of Health, show that there were 65,748 live births during 1969. This represents the second consecutive annual increase. Although this increase was less than 2 percent, it is significant in that it marks an end to the past decade's steady, persistent, decline in the number of live births, the birth rate, and also the fertility rate (Figure 1).# The reduction in the fertility

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#The vital statistics presented in this paper were obtained from various reports from the Section of Vital Statistics, Minnesota Department of Health and from the National Center for Health Statistics, U.S. Public Health Service.

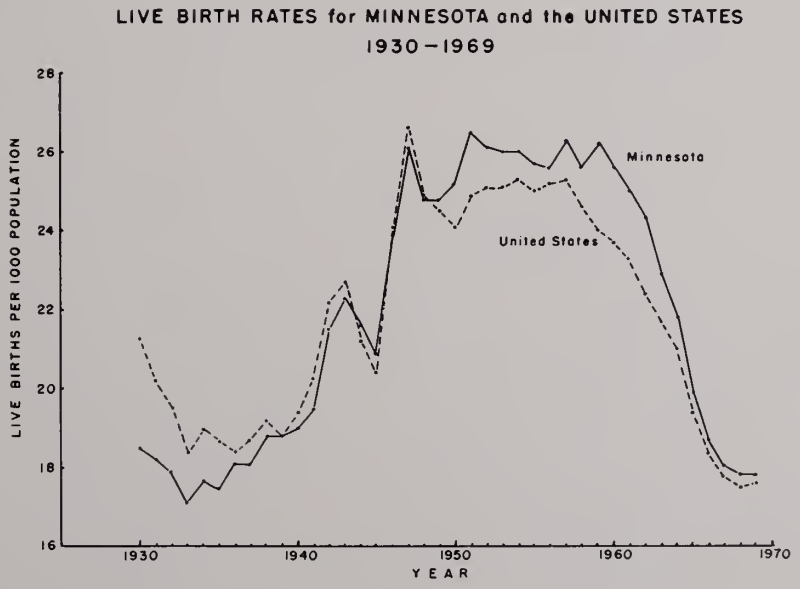


Figure 1

rate (number of live births per 1,000 women aged 15-44) has also been fairly rapid. The present rate of 93 is nearly a third less than the 1959 peak of 137.5; however, it is still substantially higher than the levels of 73 to 80 recorded during the 1930s. In contrast to the relatively high fertility rate, the present birth rate per 1,000 population approaches the low values recorded during the 1930s. The major reason the birth rate is closer to pre-war levels than the fertility rate is that the number of women of childbearing ages is now a smaller proportion of the total population than before the war (Table 1).

TABLE 1
Live Births, Birth Rates, Fertility Rates and Population: Minnesota, 1930-1968, with a Projection for 1985

	Population (Thousands)	Female Population 15-44 (Thousands)	Births	Birth Rate	Fertility Rate
1930	2,564	596	47,418	18.5	79.5
1935	2,678	625	46,034	17.2	73.7
1940	2,792	653	52,915	19.0	81.0
1945	2,618	642	54,656	20.9	85.1
1950	2,982	630	75,078	25.5	119.1
1955	3,172	637	81,532	25.7	128.0
1960	3,414	644	87,523	25.6	136.0
1965	3,558	660	70,810	19.9	107.3
1968	3,647	695	64,760	17.8	93.2
1985	4,177*	933*	87,000*	20.8*	93.2*

*Projected by Section of Vital Statistics, Minnesota Department of Health.

Ninety-seven percent of Minnesota births are white, compared to 83 percent nationwide. Although the birth rates for Negroes and Indians have decreased since 1959, as also for whites, the percentage decline for Indians and Negroes has been less than that for whites. Negro birth rates in Minnesota are nearly 50 percent higher, and Indian birth rates are more than double white birth rates. Although the fertility rate in the metropolitan area was only 12 percent greater than in the outstate area, its trend is also toward relatively higher rates. We do not have a complete explanation for the higher rates in the metropolitan area, but two factors involved are a concentration of Negro and Indian populations (which have higher birth rates) and relatively more women in the highest fertility group (age 18-29) compared to other childbearing ages.

These factors, higher fertility rates among urban dwellers in increasingly urbanized society, plus an apparent upward trend in birth rates, are of considerable concern in planning for the health and welfare of the State. There is increasing public concern and increasing demand on agencies, both public and private, for family planning information and services. Response to this public demand has resulted in the development of public family planning clinics in the metropolitan areas. While the high birth and fertility rates of these areas justifies this emphasis as a basis for starting a program, the need for information may be just as critical for women living outstate as for those in the metropolitan area. The Governor's Advisory Council on Comprehensive Health Planning recommends that premarital and marital counseling and instruction

in techniques of contraception should be available to all who need these services. Improved family planning will reduce the number of unwanted babies. The importance of this goal for public health and welfare is pointed up by the results of a national study[1] which shows that although persons living in poverty have roughly the same "preferred family size," their lack of success in planning results in a fertility rate 55 percent greater than for persons not living in poverty. It is totally unreasonable that persons who can least afford to care for and raise children should have the largest families, simply because of unavailability of information concerning methods and techniques of contraception.

Illegitimacy

The number of illegitimate births has been increasing steadily. In 1955 there were 1,810 illegitimate births in Minnesota; in 1969 there were over 5,000, an increase of 180 percent in less than 15 years. The illegitimacy ratio (number of illegitimate births per 1,000 live births) has been increasing even more rapidly. In 1955 the illegitimate ratio was 22.3; in 1969 this ratio more than tripled, to 76.9. Table 2 shows the illegitimate birth rates (number of illegitimate births per 1,000 unmarried women of childbearing age) for the nation as a whole from 1950-1965.[2]

TABLE 2
Illegitimate Birth Rates per 1,000 Unmarried Women, by Age: United States[2]

	1950	1960	1965	Percent Change
15-19	12.6	15.3	16.7	+ 32.5
20-24	21.3	39.7	39.9	+ 87.3
25-29	19.9	45.1	49.3	+147.7
30-34	13.3	27.8	37.5	+182.0
35-39	7.2	14.1	17.4	+141.7
40-44	2.0	3.6	4.5	+125.0
All ages	14.1	21.6	23.5	+ 66.7

One of the more interesting observations from Table 2 is that, contrary to popular belief, it is not the teen-agers who have the greatest risk of bearing illegitimate children. In spite of the fact that nearly 45 percent of the illegitimate births occur to teen-age mothers, these women actually have the lowest illegitimacy rate for women under 40 years of age. It is also of interest to note that the rate for women over 25 years of age is increasing much more rapidly than the rate for younger girls. The usual explanation (which may or may not be true) for the increase in the illegitimacy rate is that the incidence of premarital intercourse has increased. However, several other factors may also be involved, such as a decline in induced abortions, a reduction of the sterility associated with venereal disease, and increased fecundity due to improved nutrition. It would be virtually impossible to determine the relative influence of these various factors.

The increase in illegitimacy poses problems for public health and welfare agencies. The social costs are substantial and justify increased efforts of public agencies to help prevent further unwanted pregnancies. Provision of family life and sex education, for parents as well as for students, by competent instructors may be helpful. Education in sex and family life should include emphasis on the moral and social responsibilities of parenthood, as well as basic anatomical information.

Congenital Anomalies

The reporting of congenital anomalies observable at birth is too recent to demonstrate any trend, if such exists. Accurate completion of the confidential medical section of the birth certificate by attending physicians is providing valuable current data not otherwise readily available for analysis. These reports also provide a basis for early case finding by the State Health Department, with follow-up as indicated (Table 3).

Cytogenetic* studies as an aid in diagnosis of chromosomal and metabolic abnormalities are available from the State Health Department. Genetic consultation to physicians and counseling to parents on the risks of reoccurrence are also provided.

TABLE 3
Congenital Anomalies by Age of Mother
Live Births Occurring in Minnesota, 1967

		Age of Mother						
Congenital Anomalies	Total	Under 20	20-24	25-29	30-34	35-39	40-44	45 & Over
Anencephalus	12	3	5	2	1	1	—	—
Spina Bifida with Hydrocephalus	4	1	—	2	—	1	—	—
Spina Bifida without Hydrocephalus	44	4	18	13	2	7	—	—
Hydrocephalus	14	2	4	4	1	1	2	—
Other Nervous System Anomalies	6	—	1	3	1	1	—	—
Eye Anomalies	15	1	7	1	4	—	1	1
Ear, Face & Neck Anomalies	29	5	7	11	1	4	—	1
Heart Anomalies	85	6	30	21	15	12	1	—
Other Circulatory System Anomalies	12	1	6	2	1	2	—	—
Respiratory System Anomalies	7	—	5	1	1	—	—	—
Cleft Palate—Cleft Lip	96	10	28	33	15	7	2	1
Digestive System Anomalies	60	10	12	19	9	9	1	—
Indeterminate Sex-Undescended Testicle	30	1	12	8	7	1	1	—
Hypospadias	65	7	24	19	11	3	1	—
Other Genital Organ Anomalies	39	5	12	9	7	5	1	—
Urinary System Anomalies	26	3	7	10	5	1	—	—
Clubfoot	111	12	41	26	18	12	1	1
Polydactyly	52	3	26	10	9	2	2	—
Syndactyly	32	—	9	15	5	3	—	—
Reduction Limb Deformities	15	2	5	7	1	—	—	—
Other Limb Anomalies	70	8	31	18	7	4	2	—
Other Musculoskeletal System Anomalies	49	7	16	17	6	1	2	—
Skin, Hair & Nail Anomalies	30	5	9	7	6	3	—	—
Other Specified Anomalies	3	—	1	—	1	—	1	—
Unspecified Anomalies	21	2	8	7	3	1	—	—
Situs Inversus—Conjoined Twins	3	1	—	—	1	—	1	—
Down's Disease	79	2	13	8	14	19	20	3
Other Multiple System Anomalies	20	1	9	5	3	2	—	—
TOTAL	1,029	102	346	278	155	102	39	7
Total Births With Anomalies	876	88	295	239	130	86	33	5
Total Births	64,331	7,167	23,771	17,734	9,136	4,816	1,599	97
Anomaly Rate per 1,000 Births	13.6	12.3	12.4	13.5	14.2	17.9	20.6	51.5

Perinatal Mortality

Perinatal mortality is loosely defined as loss of the fetus or infant prior to, during, or following delivery. A fetal death is a death prior to the complete expulsion or extraction of a product of conception from its mother, irrespective of the duration of pregnancy. In Minnesota, only those fetal deaths of 20 or more weeks of gestation are reportable. We define perinatal deaths as fetal deaths of 20 weeks or more gestation, plus infant deaths during the

*See Test Your Word Score, page 753.

first four weeks of life. Some investigators include only fetal deaths of 28 weeks or more gestation, plus infant deaths during the first week of life. Infant deaths occurring during the first four weeks of life are referred to as neonatal deaths. Because of differences in reporting fetal deaths and live births, perinatal mortality rates are better than infant mortality rates as a measure of health conditions of different areas. However, comparisons may still be questionable, since completeness of reporting varies (Table 4).

TABLE 4

Infant and Neonatal Deaths by Cause
Minnesota Residents, 1967

Cause of Death	Infant Deaths	Neonatal Deaths
All Causes—Total	1,288	980
Certain diseases of early infancy—Total	793	783
Immaturity (with other subsidiary conditions or unspecified)	187	186
Ill-defined diseases peculiar to early infancy	197	195
Postnatal asphyxia and atelectasis	157	156
Injury at birth, intracranial-spinal and other	155	154
Infections of the newborn	41	38
Hemolytic diseases of the newborn (erythroblastosis)	33	33
Neonatal disorders arising from certain diseases of the mother during pregnancy	18	17
Hemorrhagic disease of the newborn	4	4
Nutritional maladjustment	1	—
Congenital malformations—Total	237	151
Diseases of the respiratory system—Total	83	1
Pneumonia—influenza	51	—
Lobar pneumonia	(9)	(—)
Bronchopneumonia	(16)	(—)
Primary atypical pneumonia	(18)	(—)
Pneumonia, other and unspecified	(8)	(—)
Pulmonary congestion and hypostasis	19	1
Bronchitis	2	—
Other diseases of the respiratory system	11	—
Ill-defined causes	56	7
Accidents, poisonings and violence—Total	43	8
Motor vehicle accidents	9	—
Accidental falls	8	—
Accidental mechanical suffocation in bed or cradle	4	—
Inhalation and ingestion of food causing obstruction or suffocation	3	1
Foreign body entering other orifice	3	1
Accidental drowning	2	1
Inhalation and ingestion of other object causing obstruction or suffocation	1	—
Accidents caused by electric current	1	—
Accidents caused by fire	1	—
Excessive heat	1	1
Other and unspecified accidents	5	1
Infanticide	5	3
Diseases of the digestive system—Total	23	11
Gastroenteritis and colitis, except ulcerative, age 4 weeks and over	6	—
Hernia of abdominal cavity	11	8
Other diseases of the digestive system	6	3
Diseases of the nervous system and sense organs—Total	20	5
Meningitis (except meningococcal or tuberculous)	10	4

(Continued to next page)

TABLE 4 (Continued)

Cause of Death	Infant Deaths	Neonatal Deaths
Malignant neoplasms	8	3
Infective and parasitic diseases	7	1
Meningococcal infections	2	—
Granulomatous disease	1	—
Moniliasis	1	1
Septicemia	1	—
Virus infection	1	—
Whooping cough	1	—
Allergic, endocrine system, metabolic, and nutritional diseases	5	3
Mental deficiency	5	5
Diseases of the circulatory system	4	1
Hemangioma	1	1
Inborn defect of muscle	1	—
Infection of kidney	1	—
Ulcer of skin	1	—

Fetal Deaths

Only a few states have required reporting of early fetal deaths (less than 20 weeks gestation) and such reports have been considered incomplete. Preliminary findings indicate a ratio of eight early fetal deaths to 100 live births. In the two large public hospitals in Minneapolis and St. Paul the ratio approximated 10, while in the other hospitals surveyed the ratios ranged from 2 to 6. In 1952 Erhardt[3] studied fetal deaths in New York City where physicians were required to report all products of conception. A ratio of 8.2 early fetal deaths to 100 live births was reported, approximately equal to the results of the Minnesota study.

Neonatal Deaths

The rate for neonatal deaths (deaths of live-born infants within 28 days of birth) follows a downward trend very similar to that for fetal deaths, with the Minnesota rate always lower than the nationwide rate. The Minnesota rate declined to an estimated 1969 level, 39 percent below that for 1930, an indication of improvement in the health of the Minnesota infants (Figure 2).

Because of the similarity of the fetal death and the neonatal death trends, the perinatal death trend would also necessarily be similar. Neonatal death rates have decreased in the white and Indian populations. The Negro rate, however, which was comparable to the white rate in 1950, has since increased 45 percent, probably because of the recent migration of Negroes from the South.

Infant Deaths

The infant mortality rate has been traditionally used as a valid index of the health status of a community and as a measure of the adequacy of health services. It is still useful even though socioeconomic factors are now recognized as equally potent factors. Minnesota has one of the lowest infant mortality rates among all the States. For the past two years the Minnesota rate

has been below 20 per 1,000 live births.

Preventive services include two-week refresher courses for hospital nurses employed in newborn and premature care, and regional seminars reaching more than 700 nursing staff members of hospitals and health agencies. Also, in 1969 the State Health Department performed more than 74,000 Guthrie screening tests for early identification of phenylketonuria.

Maternal Mortality

During recent years, the number of maternal deaths in Minnesota has varied between five and 15 per year; the average maternal mortality rate in Minnesota is about 14 per 100,000 live births. While there has been no decline in this rate in the past decade, the contrast with earlier decades is striking. In 1930,

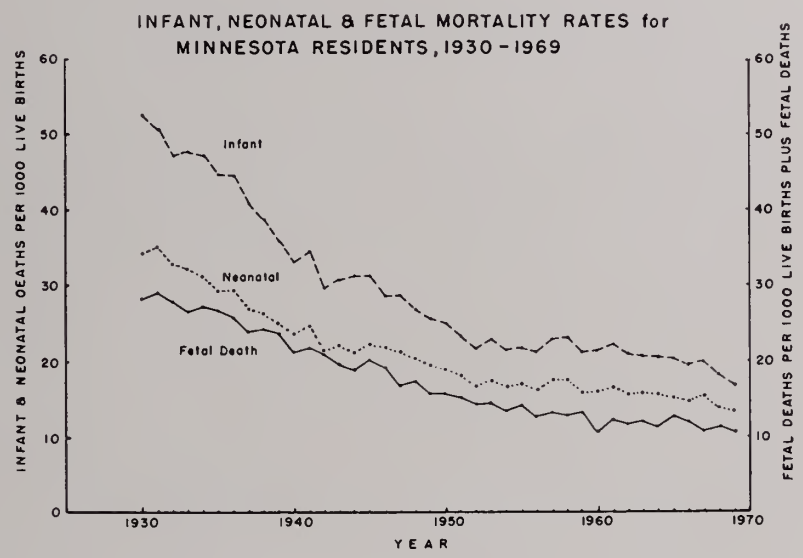


Figure 2

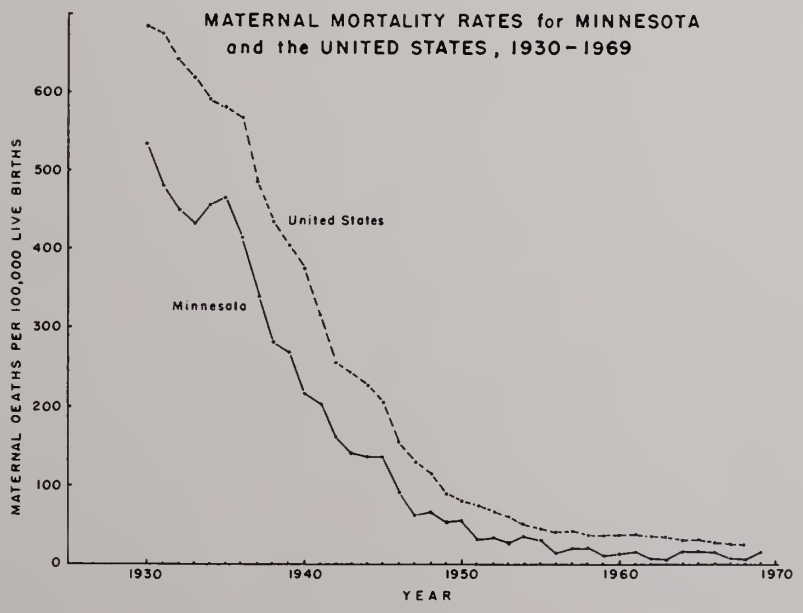


Figure 3

for example, one mother out of 200 died from maternal causes; today there is only one death per 7,000 mothers.

The Minnesota rate has been consistently below the national rate for many years. During the 1930s it was about 75 to 80 percent of the national rate; today it is roughly half the national rate, indicating an improvement in our relative standing as well as in the rate itself. It is obvious, therefore, that there has been significant betterment in maternal health, the primary reasons being improved prenatal, obstetric, and postnatal care, higher standards of living, better nutrition, new drugs and antibiotics, improved and more accessible hospital care. The activities of the Maternal Mortality Study Committee have had a large influence (Figure 3).

Because of the small number of deaths each year, it is necessary to combine data for a number of years to obtain any significant information concerning causes of maternal death. During the 10-year period, 1958-1967, there were a total of 127 maternal deaths. Table 5 shows maternal deaths by cause for these years. One third of these deaths were due to complications of pregnancy; over one fourth to complications of delivery; one fifth to abortion; and about one sixth to complications of the puerperium. While the total number of recorded abortion deaths in Minnesota during the period 1958-1967 was only 25, this is 20 percent of all maternal deaths. Modernization of Minnesota's laws on abortion to enable qualified physicians to exercise sound medical judgment would almost certainly result in further reduction of maternal mortality.

TABLE 5
Maternal Deaths by Cause
Minnesota, 1958-1967

	ICD Code	Number	Percent
Complications of Pregnancy	640-649	42	33.1
Pyelitis and Pyelonephritis of Pregnancy	640	(1)	0.8
Toxemias of Pregnancy	642	(20)	15.7
Hemorrhage of Pregnancy	644	(2)	1.6
Ectopic Pregnancy	645	(6)	4.7
Other Complications of Pregnancy	648	(13)	10.2
Abortion	650-652	25	19.7
Without Mention of Sepsis or Toxemia	650	(11)	8.7
With Sepsis	651	(13)	10.2
With Toxemia, No Mention of Sepsis	652	(1)	0.8
Delivery without Mention of Complication	660	2	1.6
Delivery with Specified Complication	670-678	36	28.3
Placenta Previa or Antepartum Hemorrhage	670	(8)	6.3
Retained Placenta	671	(2)	1.6
Other Postpartum Hemorrhage	672	(7)	5.5
Abnormality of Bony Pelvis	673	(1)	0.8
Prolonged Labor of Other Origin	675	(1)	0.8
Other Trauma	677	(5)	3.9
Other Complications	678	(12)	9.4
Complications of the Puerperium	680-689	22	17.3
Sepsis of Childbirth	681	(7)	5.5
Puerperal Phlebitis and Thrombosis	682	(4)	3.1
Puerperal Pulmonary Embolism	684	(3)	2.4
Puerperal Eclampsia	685	(1)	0.8
Cerebral Hemorrhage	687	(4)	3.1
Other Complications of Puerperium	688	(3)	2.4
Total Maternal Deaths	640-689	127	100.0

The maternal mortality rate in Minnesota as well as in the United States increases with the age of the mother. The five-year average (1963-1967) age-specific maternal mortality rate for Minnesota for mothers under 30 years of age was 6.5 per 100,000 live births. For mothers 30 through 39 years the rate was four times higher (26.5), and for mothers 40 years or older it was 12 times (76.1) the rate in the age group under 30 years. It should be noted that the number of maternal deaths due to delivery or the complications of pregnancy, childbirth, or the puerperium as defined by the International Classification of Diseases is about one third of the deaths included in the maternal mortality study conducted by the Minnesota State Medical Association in cooperation with the Minnesota Department of Health. In addition to deaths due directly to the above obstetric causes, the Medical Association study includes all female deaths associated with, but not necessarily due to, obstetric causes, for a 90-day postpartum period.

Summary

1. Provisional statistics for the number of live births during 1969 indicate the second consecutive annual increase in the number of live births.

2. The increase in the number of live births during 1968 and 1969 marks an end to the past decade's steady, persistent decline in the number of live births, the birth rate, and also the fertility rate.

3. Birth rates and fertility rates vary considerably within the State. In 1967 birth rates ranged from a low of 11.8 per 1,000 population in Kittson and Lac Qui Parle Counties to highs of 26.0 in Scott County and 25.9 in Anoka County. Fertility rates varied from a low of 61.5 per 1,000 females aged 15-44 in Kittson County to a high of 141.3 in Lake of the Woods and 130.5 in Anoka County.

4. The birth rate for the seven-county metropolitan area is 22 percent higher than for the remainder of the State, and the trend is toward greater differences.

5. Higher fertility rates among urban dwellers in an increasingly urbanized society, plus an upward trend indicated in birth rates, are of considerable concern in planning for the health and welfare of the State.

6. The number of illegitimate births has increased 180 percent in less than 15 years; the illegitimate ratio (number of illegitimate births per 1,000 live births) has more than tripled since 1955. On a nationwide basis the illegitimacy rates (number of illegitimate births per 1,000 unmarried women of childbearing age) have increased for all age groups, but the increase is substantially less, on a percentage basis, than the increase in the illegitimacy ratios. The risk of having an illegitimate child is greater for older women than for teen-agers.

7. Congenital anomalies occurred more frequently in infants of mothers who had some complication, whether related to pregnancy or not. The rate for anomalies in infants of mothers with hydramnios as a complication has been ten times greater than in those without hydramnios as a complication. Down's disease occurs almost 50 times more frequently in infants born to mothers over 40 years of age than in those of young mothers under 20.

8. Fetal death rates, neonatal death rates, and infant death rates have all declined since 1930, with a leveling off in the 1950s. The drop since 1930 has been 38 percent for the fetal death rate, 39 percent for the neonatal rate, and 32 percent for the infant death rate. Despite this drop there were 712 fetal

deaths and 1,288 infant deaths in 1967, totaling 2,000 deaths in all.

9. The average maternal mortality rate in Minnesota is about 14 per 100,000 live births. While there has been no decline in the maternal mortality rate in the past decade, the contrast with earlier decades is striking. In 1930, for example, one mother out of 200 died from maternal causes, while today there is only one death per 7,000 mothers.

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1. Campbell, A. A.: The Role of Family Planning in the Reduction of Poverty. J. Marriage Fam 30:236, 1968.
2. National Center for Health Statistics, Trends in Illigitimacy, United States, 1940-1965. Vital and Health Statistics 21:15, 1968.
3. Erhardt, C. L.: Reporting of Fetal Deaths in New York City. Public Health Reports 67: 1161, 1952.

Samuel W. Robinson, M.D.

"Pink Sand" is a water color, painted in 1968 at Harbour Island, Bahamas, on the Atlantic Beach side of Harbour Island. Harbour Island is just off the northern tip of Elenthera. The pink sand is seen at water's edge along Elenthera but particularly on Harbour Island and is more impressively pink after being washed by each wave. On this beach coral has added some faint color flecks to the sand which gives the beach a bit of a pink glow.

This painting won first prize in water color in 1968 at the exhibition of the American Physicians Art Association, which show is held in conjunction with the American Medical Association.

Dr. Robinson is a practicing physician in Columbus, Ohio.

Fat Chance

Let's say you have a patient who
Eats more than anyone, or two,
And of the many things she eats
Most loves to gorge on starches, sweets.
Now you could tell her she is lacking
In self-control, and have my backing,
Or make her switch, if all else fails,
To biting on her fingernails.
Or you could say, "Now don't you fuss,
It's naughty hypothalamus,
No fault of yours." She'd love you dearly,
And get to weigh a ton, or nearly.*

*Richard Armour: The Medical Muse, 1963.

Remember

Those dry martinis were too much for me...
Last night I really felt immense,
Today I feel like thirty cents;
It is no time for mirth and laughter
In the cold gray dawn of the morning after.—George Ade

I love my family.
I adore this house.
My in-laws are great.
The neighbors are wonderful.



Indications: For use in management of anxiety and tension occurring alone or as accompanying symptom complex to medical and surgical disorders and procedures. Though not a hypnotic, fosters normal sleep through antianxiety and related muscle-relaxant properties.

Contraindications: History of sensitivity to meprobamate.

Important Precautions: Carefully supervise dose and amounts prescribed, especially for patients prone to overdose themselves. Excessive prolonged use has been reported to result in dependence or habituation in susceptible persons, as alcoholics, ex-addicts, and other severe psychoneurotics. After prolonged excessive dosage, reduce dosage gradually to avoid possibly severe withdrawal reactions. Abrupt discontinuance of excessive doses has sometimes resulted in epileptiform seizures.

Warn patients of possible reduced alcohol tolerance, with resultant slowing of reaction time and impairment of judgment and coordination.

Reduce dose if drowsiness, ataxia or visual disturbance occurs; if persistent, patients should not operate vehicles or dangerous machinery.

Side Effects include drowsiness, usually transient; if persistent and associated with ataxia, usually responds to dose reduction; occasionally concomitant CNS stimulants (amphetamine, mephentermine sulfate) are desirable. Allergic or idiosyncratic reactions are rare, but such reactions, sometimes severe, can develop in patients receiving only 1 to 4 doses who have had no previous contact with meprobamate. Previous history of allergy may or may not be related to incidence of reactions. Mild reactions are characterized by itchy urticarial or erythematous maculopapular rash, generalized or confined to groin. Acute nonthrombocytopenic purpura with cutaneous petechiae, ecchymoses, peripheral edema and fever have been reported. One fatal case of bullous dermatitis following intermittent use of meprobamate with prednisolone has been reported. If allergic reaction occurs, meprobamate should be stopped and not reinstituted. Severe reactions, observed very rarely, include angioneurotic edema, bronchial spasms, fever, fainting spells, hypotensive crises (1 fatal case), anaphylaxis, stomatitis and proctitis (1 case) and hyperthermia. Treat symptomatically as with epinephrine, antihistamine and possibly hydrocortisone. Aplastic anemia (1 fatal case), thrombocytopenic purpura, agranulocytosis and hemolytic anemia have occurred rarely, almost always in presence of known toxic agents. A few cases of leukopenia, usually transient, have been reported on continuous administration.

Meprobamate may sometimes precipitate grand mal attacks in patients susceptible to both grand and petit mal. Extremely large doses can produce rhythmic fast activity in the cortical pattern. Impairment of accommodation and visual acuity has been reported rarely. After excessive dosage for weeks or months, withdraw gradually (1 or 2 weeks) to avoid recurrence of pretreatment symptoms (insomnia, severe anxiety, anorexia). Abrupt discontinuance of excessive doses has sometimes resulted in vomiting, ataxia, tremors, muscle twitching and epileptiform seizures. Prescribe very cautiously and in small amounts for patients with suicidal tendencies. Suicidal attempts have resulted in coma, shock, vasomotor and respiratory collapse and anuria. Excessive doses have resulted in prompt sleep, reduction of blood pressure, pulse and respiratory rates to basal levels, and occasionally hyperventilation. Treat with immediate gastric lavage and appropriate symptomatic therapy. (CNS stimulants and pressor amines as indicated). Doses above 2400 mg./day are not recommended.

Composition. Tablets, 200 mg. and 400 mg. meprobamate. Coated Tablets, WYSEALS® EQUANIL (meprobamate) 400 mg. (All tablets also available in REDIPAK® [strip pack], Wyeth.) Continuous-Release Capsules, EQUANIL L-A (meprobamate) 400 mg.

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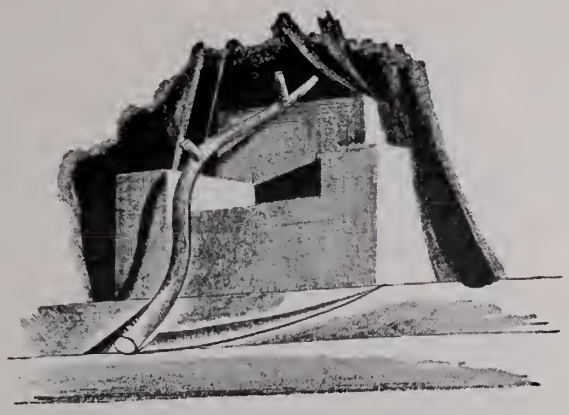
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In Memoriam

Death, so called, is a thing which makes men weep,
And yet a third of life is pass'd in sleep.

—Byron

DONALD S. BRANHAM, M.D.

Dr. Donald S. Branham, 77, former Albert Lea physician, died March 25. A native of Minneapolis, Dr. Branham practiced for many years in Albert Lea before heading up the medical service at St. Peter State Hospital.

He was a member of the American Medical Association, the Nicollet-LeSueur County Medical Society, American Psychiatric Association, Association of Military Surgeons of the United States and an Associate Member of the Minnesota State Medical Association.

Dr. Branham is survived by his wife and son.

GEORGE M. FREDERICKS, M.D.

Dr. George M. Fredericks, 68, Minneapolis physician, died April 1. Born in Minneapolis, Dr. Fredericks later attended the University of Nebraska Medical School from which he received his medical degree.

He was a member of the American Medical Association, Hennepin County Medical Society and the Minnesota State Medical Association

WILLIAM W. LIFFRIG, M.D.

Dr. William W. Liffrig, 70, Red Wing physician, died December 27. Born in Mazeppa, Minnesota, Dr. Liffrig obtained his medical education at the Northwestern University Medical School in Chicago.

He was a member of the American Medical Association, the Goodhue County Medical Society and an Associate Member of the Minnesota State Medical Association.

He is survived by his wife.

LEON A. STEFFENS, M.D.

Dr. Leon A. Steffens, 74, Red Wing physician, died April 4. Born in Chicago, Illinois, Dr. Steffens attended the University of Chicago and the University of Minnesota Medical School.

He was a member of the American Medical Association, the Goodhue County Medical Society, Red Wing Masonic Lodge, the Shriners, the Goodhue County Association for Mentally Retarded and a Life Member of the Minnesota State Medical Association. Dr. Steffens was to have been honored as a 50 Club Member at the annual meeting of the Minnesota State Medical Association in Duluth in May.

He is survived by his wife and son.

RUBY JANE SMITH-VEIRS, M.D.

Dr. Ruby Veirs, 80, specialist in obstetrics, died April 4. A native of Vernon, Texas, Dr. Veirs graduated from the Medical Department of the University of Louisville, Kentucky.

She was a member of the St. Paul Zonta Service Club, Ramsey County Medical Society, the American Medical Association, the Pan American Women's Medical Association and an Associate Member of the Minnesota State Medical Association. Dr. Veirs was to have been honored as a 50 Club Member at the Minnesota State Medical Association's Annual Meeting in May.

Dr. Veirs is survived by her husband, Dr. Dean Veirs of Hastings and her daughter.

ARLIE R. BARNES, M.D.

Dr. Arlie R. Barnes, 77, specialist in diseases of the heart and member of the Mayo Clinic staff for 32 years before retiring in 1957, died unexpectedly March 24 in Panama City, Florida. He was a former president of the American Heart Association and onetime chairman of the Clinic's Board of Governors.

Born at Paris Crossing, Indiana, Dr. Barnes received his doctor of medicine cum laude from Indiana University.

In 1956 the American Heart Association presented him with the Gold Heart Award, and the next year he was awarded a certificate of merit from the University of Minnesota in recognition of his long service as a member of its graduate faculty in the Mayo School.

He was a member of the American Medical Association, the Zumbro Valley Medical Society and an Associate and 50 Club Member of the Minnesota State Medical Association.

He is survived by his wife and son.

THEODORE P. MOLLERS, M.D.

Dr. Theodore P. Mollers, 65, Minneapolis physician, died March 31. Born in Lakeville, Minnesota, Dr. Mollers attended the University of Minnesota Medical School.

He was a member of the American Medical Association and the Hennepin County Medical Society and an Associate Member of the Minnesota State Medical Association.

Dr. Mollers is survived by his wife.

JOSEPH A. PRIM, M.D.

Dr. Joseph A. Prim, 96, Minneapolis physician for over 70 years, died May 11. Born in Scandia, Minnesota, Dr. Prim graduated from the University of Minnesota Medical School.

He was a member of the American Medical Association and the Hennepin County Medical Society and a Life Member of the Minnesota State Medical Association.

Dr. Prim is survived by his wife and daughter.

Committee

Metropolitan Council

Creative Government, Comprehensive Health Planning, and the Medical Community

Readers of *Harpers'*, *Time* and *City* magazines are aware of the national publicity which our area has received for what John Fischer has termed the "Minnesota Experiment," or the Metropolitan Council, as the planning and coordinating body in the seven-county Twin Cities metropolitan area. Created by the State Legislature in 1967, endorsed and strengthened by the 1969 Legislature, the Metropolitan Council is currently engaged in such major issues as metropolitan finance, development centers, airport siting, sewers, thoroughfare and transit systems, open space, housing, and criminal justice. It is also involved in comprehensive health planning.

The Comprehensive Health Planning Law, Public Law 89-749, was passed in partial response to the so-called "health care crisis." Popular periodical and professional journals constantly inform the reader about the crisis in health care delivery and the need to encourage efficiencies, incentives, improved planning, and other reforms without discarding the essentially private, non-governmental nature of the system.

The Comprehensive Health Planning Advisory Committee was asked to "recommend an organization, work program, and financing for Comprehensive Health Planning in our seven-county metropolitan area."

The nature of the health planning functions which the Comprehensive Health Planning Board will undertake, the possibility of linking health policy questions concerning manpower/services and facilities to broader issues of physical development and the social/economic implications thereof, and the "partnership" of providers *and* consumers which it establishes, warrant the interest and support of all private practitioners and the general medical public.

Committee members on a fulltime, volunteer basis—15.

*Member of Medical Advisory Committee to the Metropolitan Council.

Jane E. Hodgson, M.D.*
St. Paul, Minnesota

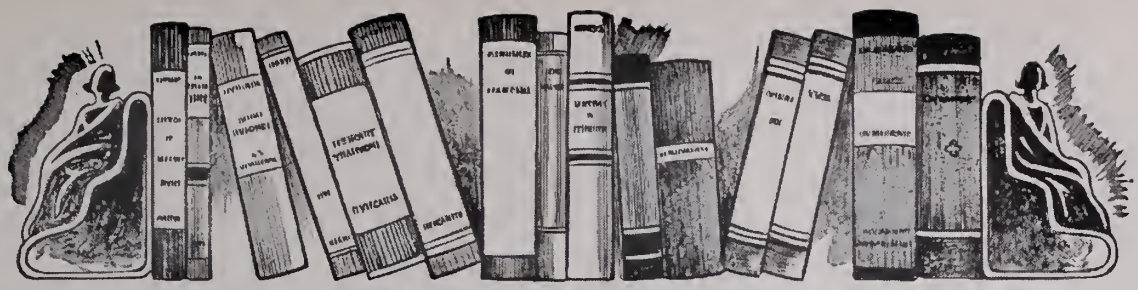
Klinefelter's Syndrome

The clinical manifestations indicate gynecomastia, small testes, aspermatogenesis and an increased excretion of follicle-stimulating hormone. The urinary hormonal pattern is compatible to that of castrates, with a low or normal level of 17-ketosteroids and estrogens. Varying degrees of eunuchoidism may be evident. There is no known satisfactory therapy.

Durham, Robert H.—Encyclopedia of Medical Syndromes
Hoeber Medical Division, Harper and Row, New York

Idleness

Stand still and silently watch the world go by—and it will.—Anon.



Book Reviews

Books, the children of the brain.—Swift

FUNDAMENTALS OF INHALATION THERAPY. Author: Donald F. Egan. C. V. Mosby Company. Price: $11.00.

Fundamentals of Inhalation Therapy by Donald F. Egan has been written primarily for the student inhalation-therapist and the working inhalation-therapist who requires a reference for review. The book deals with fundamentals of therapy and the clinical application of inhalation therapy. These fundamentals should be understood by all physicians treating respiratory diseases for safe and effective administration of inhalation therapy, and the book serves this purpose well.

The chapters on gases and atmosphere, solutions and ions are complicated and would be understood only by the student who has acquired previous knowledge in chemistry and physics. Much of this material would not be understood by the student inhalation-therapist.

The chapter on ventilation in regard to surface tension, elastic resistance and airway resistance would demand previous knowledge in pulmonary physiology and is not aimed at the level of the student inhalation-therapist.

Dr. Egan has added a chapter on the cardiovascular system and on clinical cardiopulmonary pathology which is important since the therapist will be called upon to treat patients with both pulmonary and cardiac diseases and since the functions of the heart and lungs are so interrelated.

In the chapter on aerosol and humidity therapy, many specialists in pulmonary disease would differ on several points. Steroids by aerosol have not in our experience been of value. Prednisone does not in our experience produce bronchospasm. Wetting agents such as Alevaire and Tergemist have not in our experience been of any more value in liquefying bronchial secretions than humidification with an ultrasonic nebulizer by itself. Also we would not recommend sodium bicarbonate for its mucolytic effect, nor any of the proteolytic digestants such as Dorinase in aerosol therapy. Also we would not recommend aerosolized antibiotics, as the initial enthusiasm over their use has not been substantiated. When antibiotics are necessary, they should be used systemically.

The chapter on oxygen therapy is good and emphasizes the importance of adequate monitoring of oxygen therapy with arterial blood gases.

The book is well organized and progresses from basic fundamentals of gases and pressures, into ventilation, blood gases and acid base balance, then into therapy with aerosols and humidity, mechanical ventilation, and treatment of respiratory failure.

Emergency resuscitation is omitted but has been well described elsewhere; however, in a text of this type where emergency resuscitation is so very much a part of the care in a respiratory care unit, I think a chapter on emergency resuscitation should have been included.

David E. Dines, M.D.
Rochester, Minnesota

GREAT IDEAS IN THE HISTORY OF SURGERY. Leo M. Zimmerman and Ilza Veith. Dover Publications, Inc., New York. Price: $3.00, 587 pp., 2nd revised edition 1967.

The history of surgery is reviewed from Ancient Egypt (Papyrus Edwin Smith) to the school of Wangensteen by two well-known authorities. Excerpts from landmark papers and books are presented, discussed at length, and set in historical perspective. Thus all the great names in surgery pass in review and many lesser known ones besides. Particular emphasis is placed on the interdependence of advances in surgery and in general medicine.

The value of the book is considerably enhanced by the numerous large illustrations from original sources. This is a handsome and readable book written for professionals, but with considerable appeal to the intelligent layman as well. Dover publications deserve high praise for making this classic available to a wide audience at an attractive price.

Martin J. Beckmann, M.D.
Providence, R. I.

THE SPINE. By Bernard S. Epstein. 3rd edition, 1969. Lea and Febiger, Philadelphia, 730 pages. 482 figures. $35.00.

The latest edition of this radiological textbook and atlas has undergone extensive revision. The embryological, anatomical and functional aspects of the normal spine are again described. The significance of variations in the size and shape of the spinal canal is pointed out. Positive contrast myelography, including the technical detail, is dealt with in depth. Gas myelography, discography and cine study are also discussed.

The pathological conditions of the spine are categorized under (1) malformations, (2) diseases of congenital endocrine or metabolic origin, (3) inflammatory, degenerative and noxious diseases, (4) neoplasms, and (5) traumatic changes. In the chapter on traumatic changes, the word whiplash and the "occult" fractures of the lateral masses of cervical vertebrae are not mentioned, perhaps justifiably so. There is also an excellent chapter on diseases of the intervertebral discs. Diseases of the spinal cord and its coverings, diseases of the hematopoietic, collagen and reticuloendothelial systems, and vascular disorders are treated in additional chapters. The text is lucid and easily readable. The quality of illustrations varies from fair to excellent.

This work should remain an important reference book as well as a standard textbook for radiologists, neurologists, neurosurgeons, orthopedists, and others who are interested in diseases of the spine.

S. H. Tsai, M.D.
Minneapolis, Minnesota

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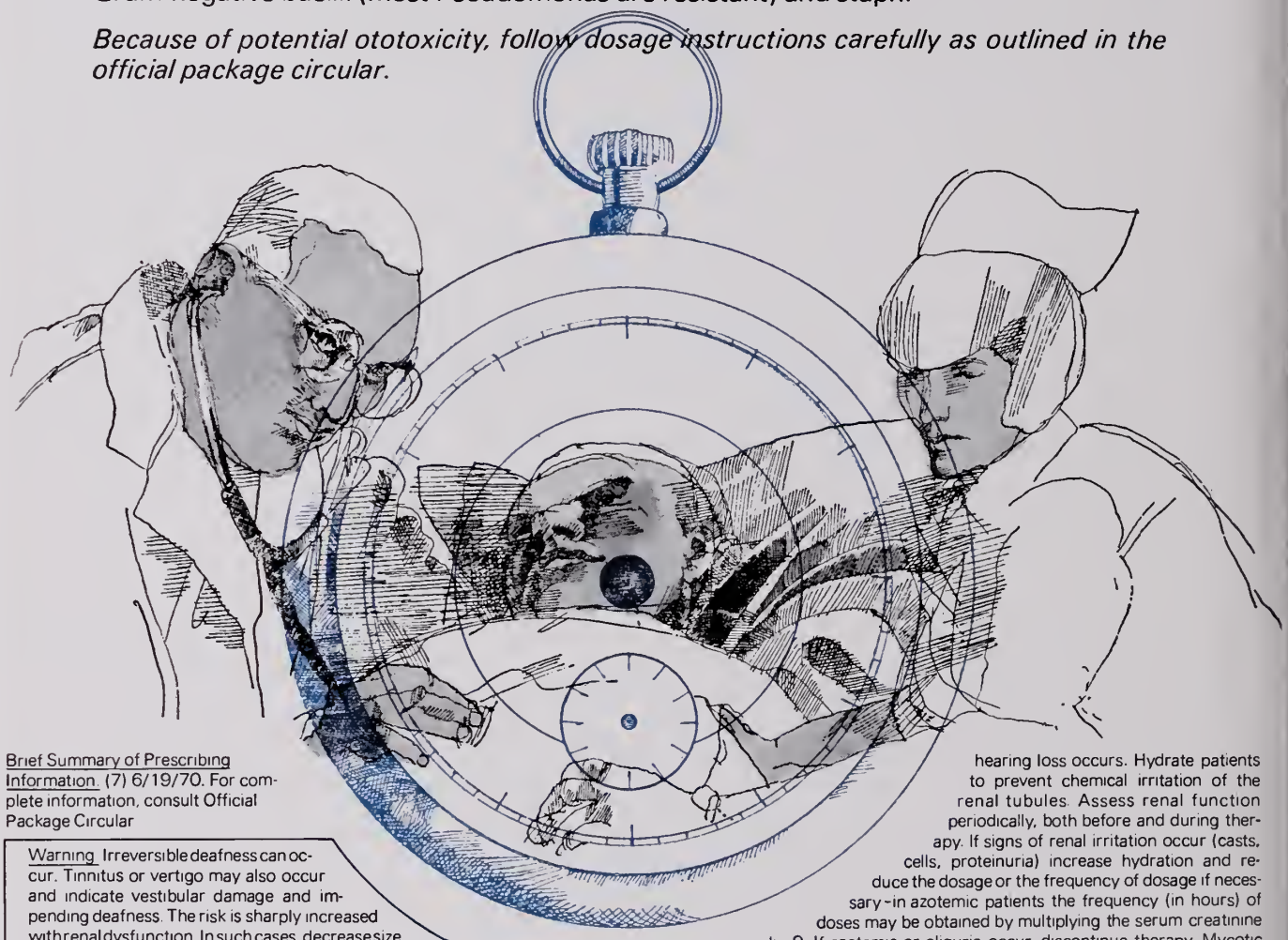
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Exercise Left Ventricular End-Diastolic Pressure

A Physiologic Indicator of Coronary Artery Disease*

CHARLES R. PETERSON, M.D.; JOHN M. HAAS, LTC, MC
ROBERT C. JONES, COL, MC

THE MOST IMPORTANT indication for selective coronary arteriography in a military hospital is to establish an accurate diagnosis when coronary artery disease is suspected. Usually the patients studied for this reason are young, have chest pain atypical of coronary artery disease, and a non-specific electrocardiographic abnormality. About one half are found to have no evidence of coronary artery disease by selective coronary arteriography; hence they provide an opportunity to study the hemodynamic abnormalities associated with coronary artery disease and to compare these findings with patients in whom no arteriographic evidence of coronary artery disease is present.

When the diagnosis of coronary artery disease is uncertain, selective coronary arteriography is the best single diagnostic test; this method, however, may not detect occluded small branches. Other studies have reported normal coronary arteriograms in patients thought to have unmistakable coronary artery disease and a lack of correlation between the post-exercise electrocardiogram and selective coronary arteriography.[1,2] Furthermore, the finding of mild irregularity or narrowing of the coronary arteries by selective coronary arteriography in a patient with atypical chest pain or a non-specific electrocardiographic abnormality does not prove the relationship.

This study was undertaken to determine which physiological measurements made at the time of selective coronary arteriography might provide reliable indicators of ischemic heart disease and support or exclude the diagnosis of significant coronary artery disease.

Materials and Methods

Thirty-seven patients (33 men and four women) had rest and exercise hemodynamic studies following completion of selective coronary arteriography; 16 patients, with an average age of 43, had no evidence of coronary artery disease by arteriography and served as the control (normal) group. Twenty-one patients, with an average age of 46, were found to have angiographic evidence of coronary artery disease; 10 of these were considered to have mild disease angiographically; nine, moderate disease; and two, severe, diffuse disease. None had valvular heart disease, radiographic enlargement of the heart, clinical evidence of heart failure, or significant hypertension.

Post-exercise electrocardiograms were recorded immediately, two minutes and five minutes after two or three times the number of trips recommended by the tables of Master, and the electrocardiograms were interpreted according to the criteria of Mattingly.[3]

Selective coronary arteriography was performed through an arteriotomy in the right brachial artery in 17 patients; in the rest the percutaneous femoral approach was employed.[4] Injections of 4-7 ml of 60% methylglucamine diatrizoate (Renografin, Squibb) were made. Filming of both coronary arteries was obtained using a rapid serial apparatus. Each patient had a 6 or 7 Fr Zucker pacemaker catheter inserted into the superior vena cava via a right antecubital vein. This catheter was advanced to the main pulmonary artery during the hemodynamic studies. All of the procedures were done, fasting, after premedication with 100 mgm secobarbital and 50 mgm meperidine intramuscularly.

*From the Division of Cardiology, Department of Medicine, Fitzsimons General Hospital, Denver, Colorado.
Dr. Peterson is presently practicing at the St. Louis Park Medical Center, Minneapolis.
Requests for reprints should be addressed to Col. Robert C. Jones, Department of Medicine, Fitzsimons General Hospital, Denver, Colorado.

All hemodynamic measurements were made at least 20 minutes after the last previous dose of 1/150-grain sublingual nitroglycerin. No long-acting nitrates were used during the studies.

Supine exercise was accomplished with a bicycle ergometer. In patients studied from the brachial artery both legs were used on the ergometer; in those using the percutaneous femoral artery approach, only the left leg was exercised. The workload was usually 200 or 300 KPM, but patients exercised using only the left leg usually required mild assistance, probably accounting for the wide variation in the exercise oxygen consumption determinations.

Exercise oxygen consumption was measured for three minutes starting 2½ minutes after the beginning of exercise. Mean pressures were derived electronically. Left ventricular end-diastolic pressure was measured 0.04 seconds after the onset of the QRS of the electrocardiogram and a minimum of 10 measurements were averaged. When occasional premature ventricular extrasystoles were present, the resulting pressure curve and that immediately following were not measured for left ventricular end-diastolic pressure. Cardiac output was determined by the dye-dilution technique using duplicate injections of 5 mgm of indocyanine green into the pulmonary artery with sampling through the arteriography catheter while the tip was in the aortic root.

*Electronics for Medicine, White Plains, New York.

For statistical comparison of the total with the diseased groups, a method of calculating the standard error of the mean was used

Results

Rest and Exercise Hemodynamic Measurements

There was no significant difference between the normal and diseased groups of patients in the average resting cardiac index and stroke volume index. The average blood flow measurements in all groups were within normal limits (Table 1).

The average left ventricular end-diastolic pressure was abnormally elevated in the group with coronary artery disease, and the difference was highly significant, especially with exercise (left ventricular end-diastolic pressure = 19 mm Hg, P = .001). Similar but less significant elevations of pulmonary artery and pulmonary artery wedge pressures were present with exercise, indirectly reflecting the rise in left ventricular end-diastolic pressure. The average left ventricular end-diastolic pressure measurements were higher in the group with

TABLE 1
Average Hemodynamic Measurements Following Selective Coronary Arteriography

Group	VO_2/M^2		C.I. L/min/M^2		Rate Beats/min		SVI ml/m^2		Exercise Factor	Pressures, mm Hg					
										PA		PAW		LVEDP	
	Rest	Exer	Rest	Exer	Rest	Exer	Rest	Exer	Exer	Rest	Exer	Rest	Exer	Rest	Exer
NORMAL (16)	143	341	2.8	4.7	72	103	40	46	866	16	21	9	11	10	12
	±38	±200	±0.4	±0.9	±15	±13	±2	±7	±330	±6	±7	±3	±3	±3	±3
MILD (10)	149	386	2.8	4.7	78	108	36	44	864	19	24	12	13	14	16
MODERATE-SEVERE (11)	147	383	2.8	4.1	68	92	42	45	674	19	29	11	18*	14	21*
TOTAL DISEASED (21)	148	385	2.8	4.4	73	100	39	45	768	19	26	11	15	14	19
	±18	±149	±0.3	±0.7	±13	±15	±8	±6	±320	±5	±8	±3	±6	±4	±8
P	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	0.1	NSD	0.05	0.01	0.001

The numbers in parentheses indicate the number of patients in each group; VO_2/M^2 = oxygen consumption in ml/min/M^2; C.I. = cardiac index; SVI = stroke volume index; exercise factor = ml/min increase in cardiac output per 100 ml/min increase in oxygen consumption with exercise; PA = pulmonary artery; PAW = pulmonary artery wedge; LVEDP = left ventricular end-diastolic pressure; the ± values include one standard deviation; P = probability of significant difference between total control and diseased groups; NSD = no significant difference; values with asterisk (*) indicate average values of small groups that are significantly different from control (normal) group at 0.05 level of significance.

moderate or severe coronary disease (21 mm Hg) than in the group with only mild arteriographic evidence of coronary artery disease (16 mm Hg., Table 1). Two of the 16 patients in the control group had exercise left ventricular end-diastolic pressure measurements of 15 mm Hg or greater (both had measurements of 16 mm Hg), whereas 16 of 21 patients with arteriographic evidence of coronary artery disease had left ventricular end-diastolic pressure measurements of 15 mm Hg or greater (Figure 1).

The changes in cardiac index, stroke volume index, and left ventricular end-diastolic pressure associated with exercise are illustrated in Figures 2 and 3. The relationships between the change in left ventricular end-diastolic pressure and the change in stroke volume index during exercise were normal, or very near normal, in all but three of the 16 control patients.

In the groups with arteriographic evidence of *mild coronary artery disease,* four of 10 had abnormal increases in left ventricular end-diastolic pressure but a normal increase in stroke volume index (abnormal ventricular dynamics). In the group with *moderate or severe disease,* most of the patients had abnormal increases of left ventricular end-diastolic pressure with exercise, with an increase in stroke volume index; but three patients had abnormal increases in left ventricular end-diastolic pressure associated with a decrease in stroke volume index (depressed ventricular function). In this latter group, all but three patients had abnormalities in the relationships between the changes in stroke volume index and left ventricular end-diastolic pressure with exercise (Figure 3).

In the group of 21 patients with arteriographic evidence of coronary artery disease, there was no difference between the average left ventricular end-diastolic pressure values in the group with abnormal post-exercise electrocardiograms as compared to the group with normal post-exercise electrocardiograms. However, the patients considered to have classical angina pectoris had a significantly higher left ventricular end-diastolic pressure with exercise (21 mm Hg) than the group without definite angina pectoris (16 mm Hg., Table 2).

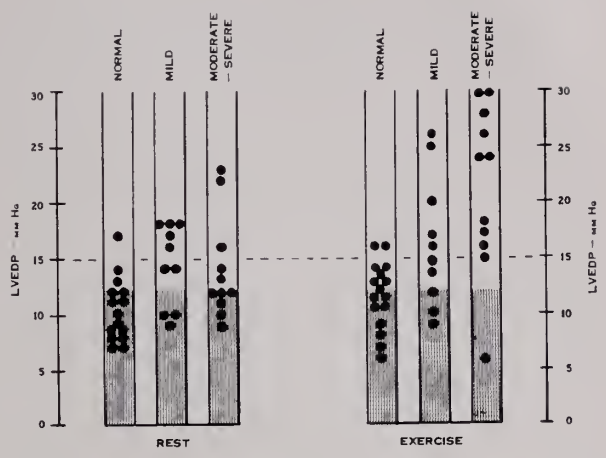


Fig. 1—Left ventricular end-diastolic pressure during rest and exercise in patients without arteriographic evidence of coronary artery disease, patients with mild coronary artery disease, and patients with moderate or severe coronary artery disease. The shaded area indicates the normal range of left ventricular end-diastolic pressure.

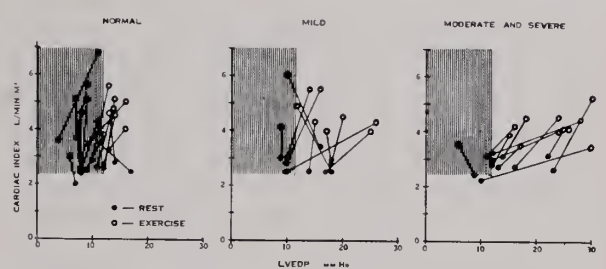


Fig. 2—Changes in cardiac index and left-ventricular end-diastolic pressure associated with exercise in patients with and without arteriographic evidence of coronary artery disease. The shaded area indicates the normal range.

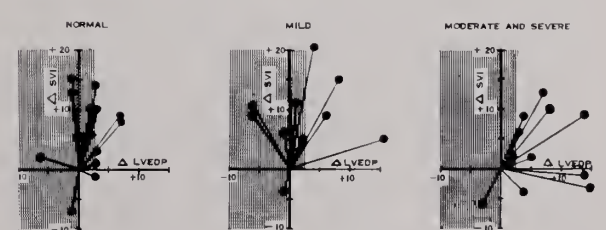


Fig. 3—Changes in stroke volume index (ml/min/M²) and left ventricular end-diastolic pressure (mm Hg) associated with exercise in patients with and without arteriographic evidence of coronary artery disease. The shaded area indicates the normal response; values in the upper right quadrant are interpreted as "abnormal ventricular dynamics", and values in the lower right quadrant are interpreted as "depressed ventricular function."[11]

TABLE 2

Comparison of Left Ventricular End-diastolic Pressure in Patients with Coronary Artery Disease According to Post-Exercise Electrocardiogram and Clinical Type of Chest Pain

	Negative Post-Exercise Electrocardiogram (12)	Positive Post-Exercise Electroconvulsive Therapy (9)	P
Rest	14.1 ± 4	13.8 ± 4	NSD
Exercise	19.5 ± 5	19.3 ± 8	NSD
	Without Definite Angina (8)	**With Definite Angina (13)**	**P**
Rest	13.9 ± 7	14.1 ± 5	NSD
Exercise	15.8 ± 7	21.1 ± 7	0.01

The numbers in parentheses indicate the number of patients in each group; P = probability of significant difference; NSD = no significant difference; the ± value includes one standard deviation; left ventricular end-diastolic pressure in mm Hg.

TABLE 3

Left Ventricular End-diastolic Pressure and Cardiac Output Before and After Selective Coronary Arteriography

LVEDP - mm Hg		C.O. - L/Min.	
Before	After	Before	After
11	16	5.4	4.6
14	16	3.7	3.8
9	13	4.3	3.9
6	8	7.1	6.0
16	22	6.2	5.6
8	10	5.9	5.7
8	10	5.1	4.7
11	12	5.7	4.7
11	15	3.7	3.8
14	14	5.8	4.7
12	16	4.0	3.8
Avg. 10.9	13.8	5.17	4.66
P 0.01		NSD	

P = probability, NSD = no significant difference

TABLE 4

Resting Hemodynamic Measurements in Ten Patients Following 1/150 Grain Sublingual Nitroglycerine

Time	8efore	3 min.	6 min.	10 min.	15 min.
Rate	71	77	80	75	70
LVSP*	141	129	120	122	127
LVEDP†	12	8	5	7	11
Mean PA‡	16	10	9	12	14
Mean Aorta	95		80		87
C.O. (L/Min.)	5.21		5.14		

*Left ventricular systolic pressure

†Left ventricular end-diostolic pressure

‡Mean pulmonary artery pressure; pressure in mm Hg.

Hemodynamic Changes Due to Coronary Arteriography and Nitroglycerine

Following selective coronary arteriography, the average left ventricular end-diastolic pressure in 11 patients increased about 3 mm Hg ($P = .01$) and the average cardiac output decreased about 500 ml/min (not a significant change) from the pre-arteriography measurements (Table 3). Following administration of sublingual nitroglycerine in 10 patients, the peak fall in left ventricular end-diastolic pressure and arterial pressures and the peak rise in heart rate occurred at six minutes without a significant change in cardiac output. By 15 minutes after nitroglycerine administration, pressures and heart rate had returned to near the pre-nitroglycerine measurements (Table 4).

Discussion

The control group for this study consisted of patients in whom coronary artery disease was suspected, but in whom no evidence of the disease could be demonstrated by selective coronary arteriography. However, a number of these patients had slight elevations of left ventricular end-diastolic pressure at rest and during exercise. It is therefore possible that some of these had mild abnormalities of left ventricular function due either to mild and angiographically undetectable coronary artery disease, or to a mild myocardiopathy from some other cause. It is of interest that about one half of the patients in the control group had nonspecific electrocardiographic abnormalities and a few had only a remote history of chest pain that was consistent with pericarditis.

Effect of Arteriography

It is possible that selective coronary arteriography produces transient abnormalities in ventricular function, even in patients without heart disease. The apparent mild increase in left ventricular end-diastolic pressure (3 mm Hg) and decrease in cardiac output (500 ml/min) following arteriography, as observed in some of the control group, may provide a partial explanation for the mild hemodynamic abnormalities noted in some of the patients in the control group. Although the change in left ventricular end-diastolic pressure was apparently statistically significant, the series is too small to

yield definite conclusions. Benchimol and McNally noted no significant hemodynamic changes following a single injection of 5 ml of 75% sodium diatrizoate into either coronary artery during a six-minute period following the injection in 11 patients;[5] however, the ischemic, chemical, or osmotic effects of multiple injections (usually 10 or 12) into the coronary circulation may be different from those of a single injection. It is also possible that the osmotic load and consequent blood volume changes associated with the administration of 100 to 150 ml of a hyperosmolar contrast agent may cause transient hemodynamic changes.

Effect of Nitroglycerine

The administration of sublingual nitroglycerine produces a significant fall in left ventricular end-diastolic pressure, the maximum effect occurring about six minutes after the administration of the drug. This effect is largely gone within 15 minutes, and in this study, where resting and exercise hemodynamic measurements were usually made 30 minutes after the last previous dose of nitroglycerine, the effect of this drug may not have significantly altered the hemodynamic determinations. On the other hand, Parker et al. have shown that nitroglycerine decreased left ventricular end-diastolic pressure both at rest and during exercise during a 15-minute period after the administration of nitroglycerine in patients with healed myocardial infarction.[6] The effect of nitroglycerine in lowering left ventricular end-diastolic pressure cannot explain the slight elevations in left ventricular end-diastolic pressure in some of the patients in the control group unless an increased venous return of transiently pooled peripheral blood occurs after the vasodilating effects are gone.

Effect of Multiple Procedures

When multiple, and possibly opposite, influences on the cardiovascular system may have been introduced during the procedure, it is impossible to explain why some of the patients in the control group had mild elevations of left ventricular end-diastolic pressure. It is possible that had the hemodynamic studies been performed prior to selective coronary arteriography, more significant differences between the control and diseased groups may have been demonstrated. The hemodynamic studies were done after arteriography because the arteriography was considered to have diagnostic priority.

Effect of Exercise

In spite of the mild hemodynamic changes that may have been induced by selective coronary arteriography or the use of nitroglycerine, and despite the fact that some of the patients in the control group may have had mild ventricular disease, significant differences in left ventricular end-diastolic pressure between the control and coronary disease groups were demonstrated by this study, especially during exercise. In the absence of significant hypertension, valvular heart disease, or any obvious myocardiopathy, a resting or exercise left ventricular end-diastolic pressure of 15 mm Hg or more tends to support the presence of ischemic heart disease, whereas an exercise left ventricular end-diastolic pressure of 12 mm Hg or less would tend to confirm the arteriographic impression of no coronary artery disease. Abnormalities of left ventricular end-diastolic pressure are more likely to be demonstrated if the patient is exercised sufficiently to increase the heart rate to at least 100 per minute, or at least double the resting oxygen consumption measurement, than if just resting measurements are made.

In patients considered to have unmistakable coronary artery disease manifested by angina pectoris, but in whom no arteriographic evidence of coronary artery disease can be demonstrated, the finding of a significantly elevated left ventricular end-diastolic pressure with exercise suggests that angiographically undetectable coronary artery disease may be present, especially if technical factors prevent optimal visualization of all major coronary arteries in at least two projections. If this explanation is considered unlikely, the presence of some other type of ventricular disease should be considered.

If a normal exercise of left ventricular end-diastolic pressure is found in a patient with angiographically demonstrable narrowing or occlusion of a coronary artery, this suggests that there is relatively effective perfusion of the myocardium. Two patients in the present study had total occlusion of a major coronary



Figure 4A



Figure 4B



Figure 4C



Figure 4D

Fig. 4—Selective coronary arteriograms from patient 32 showing total occlusion of the right coronary artery 2 cm from its origin (A). There is good filling of the posterior descending branch of the right coronary artery (arrows) via collateral vessels from the proximal right coronary artery (B) and the left anterior descending coronary artery (C and D). The left venticular end-diastolic pressure with exercise was 6 mm Hg.

artery with evidence of good collateral filling of the artery distal to the occlusion either from anastomotic vessels arising proximal to the occlusion or via collateral vessels from another coronary artery (Figures 4 and 5). Neither patient had electrocardiographic evidence of myocardial infarction. The exercise left ventricular end-diastolic pressure in these two patients was 6 and 15 mm Hg as compared to an average exercise left ventricular end-diastolic pressure of 23 mm Hg in the other nine patients in the group with moderate or severe disease. Thus exercise left ventricular end-diastolic pressure determinations may be helpful both in determining the *physiologic* need for revascularization procedures and in evaluating the *physiologic* results of such procedures. The determination of left ventricular end-diastolic pressure for this purpose has also been suggested by other similar studies.[7,8]

Patients with a history of typical angina pectoris tend to have higher levels of left ventricular end-diastolic pressure with exercise than patients without angina pectoris, or than patients with chest pain that is atypical for angina pectoris. This is consistent with other studies which have demonstrated that spontaneous or induced angina pectoris is associated with a significant rise in left ventricular end-diastolic pressure.[9,10] All patients in this study with abnormal post-exercise electrocardiograms were found to have angiographic evidence of coronary artery disease; however, this group did not have a higher average left ventricular end-diastolic pressure with exercise than patients with normal post-exercise electrocardiograms. If the type and amount of exercise used for both the electrocardiographic and hemodynamic studies had been the same, there might have been a better correlation between ischemic abnormalities of the electrocardiogram and the elevation of left ventricular end-diastolic pressure.

Measurements of cardiac output, stroke volume index, and the changes in blood flow that occur with exercise are helpful in determining whether mild or severe abnormalities of ventricular function are present. Ross et al. have used the relationships between the changes in left ventricular end-diastolic pressure and stroke volume index with exercise to distinguish between "normal ventricular function, abnormal ventricular dynamics, and depressed ventricular function."[11] In the present study of patients undergoing selective coronary arteriography a greater proportion of those with moderate and severe disease had abnormalities of ventricular function than of those with only mild coronary artery disease or no arteriographic evidence of coronary artery disease (Figure 3). Three patients in the group with moderate and severe disease had depressed ventricular function as evidenced by both an abnormal increase in left ventricular end-diastolic pressure and a fall in stroke volume index during exercise.

Abnormalities in cardiac output and the



Fig. 5—Selective coronary arteriograms from patient 34 showing subtotal occlusion of the left anterior descending coronary artery (A—top, B—bottom).

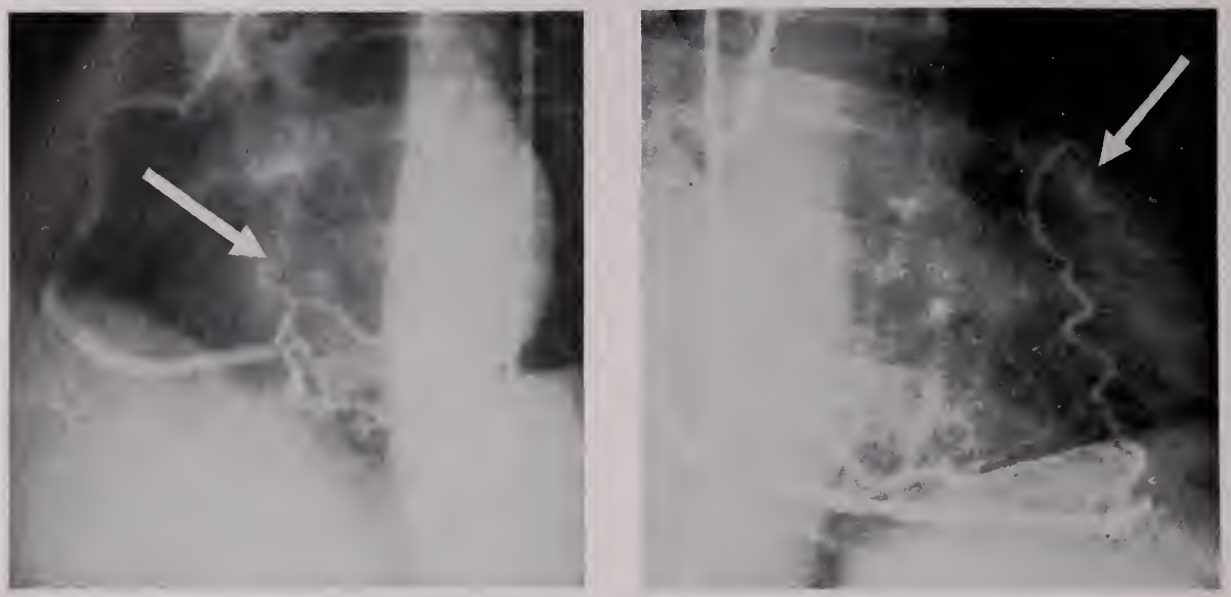


Fig. 5C (left) and 5D (right)—Good collateral filling of the distal portion of this vessel (arrows) via an anastomotic branch from the posterior descending branch of the right coronary artery (C, D). The exercise left ventricular end-diastolic pressure was 15 mm Hg.

changes in stroke volume index with exercise appear to occur only in the presence of moderately severe coronary artery disease, usually easily detectable by selective coronary arteriography; therefore such determinations probably have little value in the detection of mild coronary artery disease. Of the hemodynamic determinations used in this study, the level of left ventricular end-diastolic pressure with exercise is the most simple and reliable physiological measurement to help support or exclude the diagnosis of ischemic heart disease. Although coronary artery disease is not always associated with an elevated exercise left ventricular end-diastolic pressure, this measurement is useful in assessing the physiologic severity of ischemic heart disease.

Summary and Conclusions

Thirty-seven patients undergoing selective coronary arteriography had rest and exercise hemodynamic studies to determine which physiologic measurements made at the time of selective coronary arteriography are most useful in supporting a diagnosis of coronary artery disease and evaluating its severity. Sixteen patients had no arteriographic evidence of coronary artery disease; 10 had mild coronary artery disease, and 11 had moderate or severe, diffuse disease. Resting hemodynamic measurements were not significantly different in the two groups. Abnormalities in the change in stroke volume index during exercise were significantly abnormal only in a few patients with moderately severe disease. Of the physiological measurements used, the level of left ventricular end-diastolic pressure during exercise most consistently correlated with the presence and severity of coronary artery disease. A relatively normal left ventricular end-diastolic pressure in the presence of significant coronary obstruction appeared to be associated with arteriographic evidence of good collateral circulation beyond the obstruction. Patients with definite angina pectoris had a higher average level of left ventricular end-diastolic pressure during exercise than patients with atypical chest pain or absence of chest pain. It is concluded that a left ventricular end-diastolic pressure during exercise of 15 mm Hg or more tends to support the diagnosis of coronary artery disease, and a measurement of 12 mm Hg or less tends to support an arteriographic impression of no coronary artery disease. In the absence of other types of heart disease, the level of left ventricular end-diastolic pressure with exercise is useful in assessing the physiological severity of coronary artery disease.

References may be secured from the author or the reprints.

Low aim, not failure, is crime.—Culinary Almanac.

Antacid-Induced Phosphorus Depletion and Repletion

AZAM ANSARI, M.D.*

THE DANGERS of excessive ingestion of absorbable antacids by patients with peptic ulcer have been emphasized and widely recognized. Little or no attention, however, has been paid to the untoward effects of non-absorbable antacids. The latter are considered harmless by most physicians and may be injudiciously prescribed for prolonged periods for acid-peptic disease.

Prolonged antacid therapy with the so-called non-absorbable antacids such as aluminum hydroxide (Amphojel) and magnesium hydroxide or a combination of the two (Aludrox, Cremalin and Maalox) impairs intestinal absorption of phosphorus and may lead to serum phosphorus depletion despite its normal content in the diet. Such a depletion of serum phosphorus can produce skeletal harm and may cause osteomalacia.

Case Report

A 53-year-old heavy equipment operator was referred to Minneapolis Veterans Administration Hospital for diagnosis of hypercalcemia and recurrent acid-peptic disease. The patient was found to have a duodenal ulcer for which he was treating himself with large amounts of milk (1 gallon per day) and baking soda (1½ lb per month). He was proved ultimately to have chronic milk-alkali syndrome and salt-losing nephropathy. Hyperparathyroidism was excluded.

During his prolonged hospital stay he required long-term antacid treatment for healing of a duodenal ulcer. He was given a low calcium diet (300 mg per day) with a phosphorus intake of 1000 mg per day. A low Ca diet was necessary because of hypercalcemia, and phosphorus had to be restricted because it was extremely difficult for the dietitian to construct a diet low in Ca but normal in phosphorus. Rapid depletion of serum phosphorus became a perplexing problem in this patient because of the restricted intake of inorganic phosphate and the frequent intake of aluminum hydroxide containing antacids. When his serum phosphorus declined progressively and reached a low level of 1.8 mg per cent, the patient noticed weakness, lethargy, malaise and irritability. Then aluminum phosphate gel (Phosphaljel) was substituted for antacid-containing aluminum hydroxide gel. On two occasions antacid-induced phosphorus depletion by Aludrox or Amphojel and antacid-induced phosphorus repletion by Phosphaljel were demonstrated in a prolonged study conducted over 110 days (Figure).

The patient at the time of discharge was free of symptoms. His duodenal ulcer was healed and serum phosphorus and calcium remained within normal limits on a low Ca and low phosphorus diet.

Comment

Soon after the introduction of aluminum hydroxide as an antacid in the treatment of acid-peptic disease it was found that the aluminum hydroxide bound the inorganic phosphate in the gastrointestinal tract, increased phosphate excretion in the feces and thereby decreased serum phosphorus. Experimental animals have also shown similar mineral reduction when aluminum salts were ingested for several months.[1]

Osteomalacia with pseudofractures caused by the ingestion of aluminum hydroxide was first reported by Bloom[2] and his associates in 1960.

Lotz and his associates[3,4] have convincingly demonstrated the syndrome of phosphorus depletion in normal men and hypoparathyroid patients while on aluminum hydroxide and magnesium hydroxide containing non-absorbable antacids. This syndrome consists of hypophosphatemia, hypophosphaturia, increased absorption of calcium from the gut, increased demineralization of skeletal calcium and phosphorus, hypercalciuria and debility with anorexia, weakness, bone pain and malaise.

Features of this syndrome appeared in the patient reported here. The problem was compounded because in addition to a low Ca and

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low phosphorus diet he required frequent antacid intake for the relief of his ulcer symptoms. The solution was to substitute aluminum phosphate gel (Phosphaljel) because, like aluminum hydroxide gel, it has demulcent antacid and astringent properties and at the same time does not interfere with phosphate absorption.

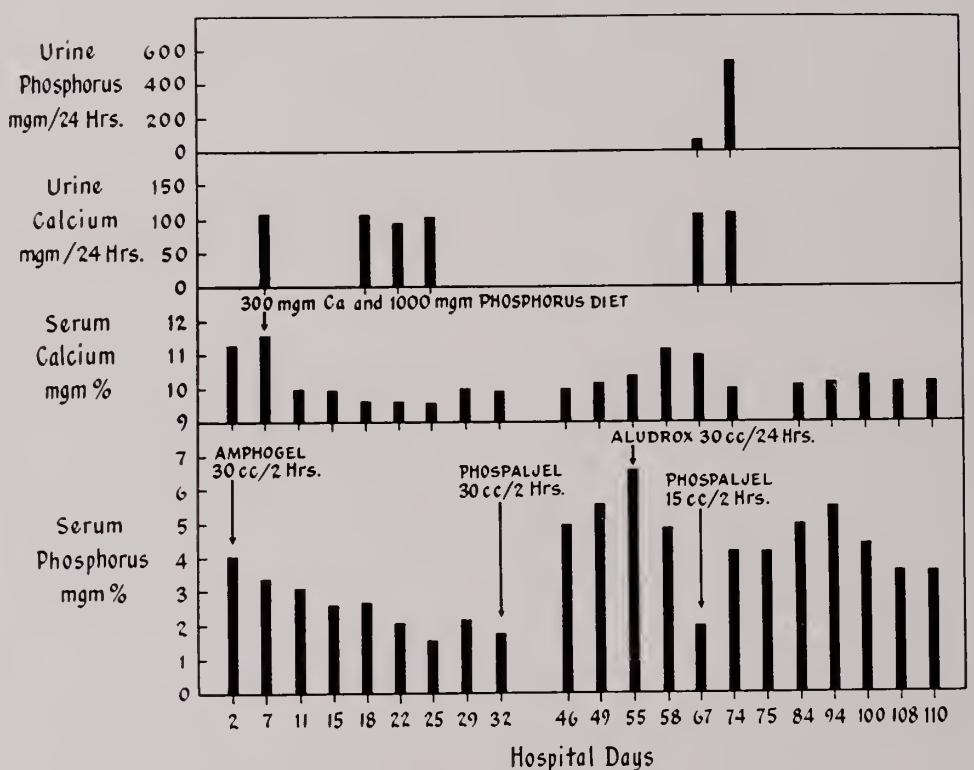
Fauley et al.[5] demonstrated the adequacy of aluminum phosphate gel in healing of peptic and jejunal ulcer both in Mann-Williamson dogs and in man. They postulated that aluminum phosphate get may be superior to aluminum hydroxide gel in the treatment of peptic ulcer patients who have diarrhea or who are on a low phosphorus diet.

References may be secured from the author or the reprints.

However, no prior studies so far have demonstrated the repletion of antacid-induced phosphorus depletion in man by aluminum phosphate gel. This was demonstrated in this patient on two occasions. The elevation of serum phosphorus above 5 mg per cent may represent a rebound phenomenon, as it slowly returned to normal without any change in therapy. However, absorption of this apparently non-absorbable antacid is another possibility.

Acknowledgment

I am indebted to Dr. Leslie Zieve, Chief, Gastroenterology Section, Veterans Administration Hospital, Minneapolis, and his staff for the opportunity to study this patient. Their continued inspiration, encouragement and guidance during the entire period of study is sincerely appreciated.



Figure—Data for G.J. while on low Ca (300 mg per day) and low phosphorus (1000 mg per day) diet for treatment of chronic milk-alkali syndrome and acid-peptic disease. Note the following: (1) Depletion of serum phosphorus while on aluminum hydroxide containing antacids (days 2 to 32 and 55 to 67). (2) Repletion of serum phosphorus with substitution of aluminum phosphate gel (days 32 to 55 and 67 to 108). The abnormal elevation of serum phosphorus during each period of repletion may represent a rebound phenomenon because serum phosphorus later became normal without any change in therapy. (3) Elevation of serum Ca during the phosphorus depletion period (days 58 to 67). (4) No change in the urinary Ca excretion during the entire period of study (days 7 to 74). (5) Decreased excretion of phosphorus in the urine during the period of depletion (day 67) and increased excretion during the period of repletion (day 74).

Pulmonary Function in Thoracic Scoliosis

Before and After Corrective Surgery

HUGH D. WESTGATE, M.D.*

From the last half of the fifth century B.C. when Hippocrates[1] first described a patient with kyphoscoliosis, interested practitioners of medicine have added to the anatomical,[2] orthopedic,[3,4,5,6,7,8] physiologic,[9] and mechanical[10,11,12,13] aspects of the disease.

Treatment of scoliosis is governed primarily by the rate of progression and the degree of the curvature, with little thought to correcting the cardiopulmonary defect, if such a defect is present. Physiotherapy, skeletal traction, spinal braces (such as the Milwaukee brace), Risser casts, and surgical measures including spinal fusion by both a transthoracic and a posterior approach and recently the Harrington[14] procedure are all accepted methods of treatment. The newer surgical procedures have been facilitated by our increased ability to handle the anesthetic and postoperative respiratory problems presented by these patients.[15,16,17]

Despite a number of detailed studies, our knowledge of the lungs in scoliosis is fragmentary. The individual with scoliosis dies of cardio-respiratory failure and not of his anatomical abnormality. At one end of the scoliotic spectrum is the young person with his peculiar breathing pattern and diminished lung volumes, but with few symptoms and continuation of normal daily activity. At the other end of the spectrum is the individual with a high-energy cost of breathing who is in ventilatory and alveolar-respiratory failure with concomitant increased pulmonary vascular resistance, secondary polycythemia and cor pulmonale. Between these two well documented extremes there exists a wide chasm in our knowledge.

The purpose of this study was to compare thoracic spinal curvature, vital capacity, maximum breathing capacity and arterial oxygen saturation before and six months, one; two and five years after correction of thoracic scoliosis by the Harrington instrumentation method.

Material

Since 1961, 74 patients with scoliosis, with or without kyphosis, have had their pulmonary function evaluated prior to the surgical procedure.

The 74 patients studied ranged in age from four to 49 years with the majority being between 13 and 22 years; 49 were females and 25 were males. Because of a selection factor in the first years of study, the sex distribution has an inherent bias.

Etiology

Of the 74 patients, 37 developed the scoliosis secondarily to poliomyelitis, and 24 cases were classified as idiopathic in nature. In another group of 13, the scoliosis was of a congenital nature, often associated with other congenital defects and diseases.

Method of Study

Surgical Procedure

All 74 patients were operated upon by the Harrington technique.[14] The posterior spinal muscles were stripped from the vertebral laminae and transverse processes over the entire length of the spinal curve. Stainless steel distracting rods hooked to the transverse processes were placed on the concave side of the curve. In some cases, contracting rods were also placed on the convex side of the curve. By placing these rods under tension, the vertebral curve was decreased. A fusion was produced by decorticating the spinous processes and laminae and inserting either bank bone or iliac crest bone. The Harrington rods maintain the scoliotic curve correction until the fusion mass is solid and are not normally removed.

Four measurements were selected for preoperative and postoperative comparison.

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See editorial, page 869.

Angle of Curvature

The angle of the curvature is an indication of the severity of the scoliosis and is most commonly the cause for the patient seeking medical attention. The angle of the curvature was measured by the method of Cobb,[3] using roentgenograms of the spine in the upright position. Previous work has made us feel that the Cobb method of measurement appears to be more practical in correlating clinical appearance with curve angulation. The apex of the curve was always in the thoracic portion of the vertebral column. The age of onset, which quite frequently was not known, and the duration of the deformity were not taken into account.

Vital Capacity

The vital capacity is made up of three of the four pulmonary volumes, (expiratory reserve volume, tidal volume and inspiratory reserve volume). The fourth volume, residual volume, has been shown to decrease in scoliosis, but not to as great an extent as the vital capacity. Any decrease in the vital capacity is, therefore, an indication of the degree of restrictive lung disease caused by the scoliosis.

Normal lung values are best predicted on the basis of height and age,[18] but after surgery it is not uncommon for patients with scoliosis to gain two or three inches in height. Such a change in height causes an inherent error which makes the observed lung volumes prior to surgery greater in proportion to the predicted volumes. If the patient gained height from surgery, his lung volumes would then be less relative to predicted values based on the new height and he would appear to have lost lung volume from surgery. Despite this distortion, our normal values were based on the patient's height and age or, if severely distorted, on age and surface area at the time of examination prior to surgery, since other methods of predicting vital capacity are probably no more accurate.[19,20]

A spirogram was recorded on a Godart Pulmotest which directly recorded tidal volume, respiratory rate, minute volume, oxygen consumption, vital capacity and its subdivisions, timed vital capacity, maximum flow rates, and maximum breathing capacity.

A closed system with carbon dioxide absorption was established with the patient in a sitting position. The recirculating pump in the Godart Pulmotest provided a resistance-free breathing system during both quiet breathing and while the maximum breathing capacity was being measured. The largest value of three trials was reported and all volumes were related to body temperature, ambient pressure, and saturation with water (B.P.T.S.).

Deviation of a single test of more than 20% from a predicted normal for both vital capacity and maximum breathing capacity is considered abnormal; however, a small deviation > 5% from a previous base study is significant.

Maximum Breathing Capacity

The maximum breathing capacity or maximum voluntary ventilation is the only test of pulmonary function which can be correlated with a patient's functional ability. The test is

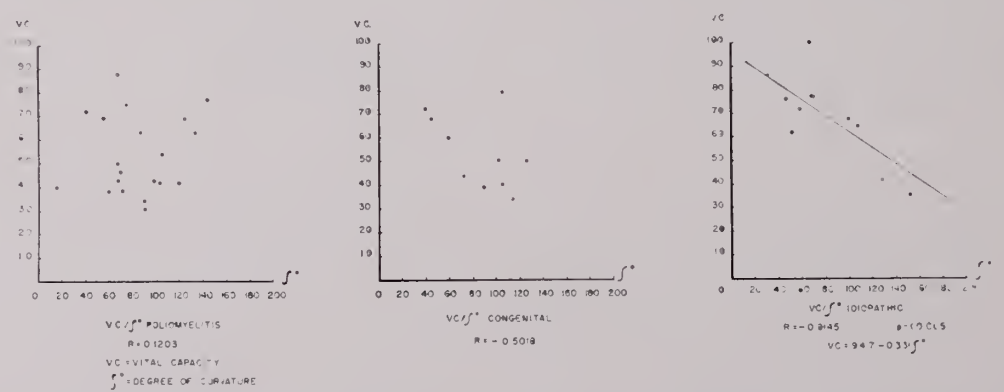


Fig. 1—Vital capacity as a percentage of normal is compared to the degree of curvature in thoracic scoliosis: (a) secondary to poliomyelitis, (b) of a congenital nature, (c) idiopathic in nature, and the significant correlation is shown in the idiopathic group.

dependent upon maximum expiratory and inspiratory flow rates, but primarily expiratory flow, and is therefore an indicator of obstructive lung disease. Maximum breathing capacity was recorded for a 15-second period on the Godart Pulmotest and then converted to liters per minute (L/min. B.P.T.S.).

Arterial Oxygen Saturation

The arterial oxygen tension, or to a lesser degree arterial saturation, indicates the efficiency and evenness of ventilation and perfusion. If areas of the lung are poorly ventilated but well perfused, the arterial oxygen tension (PaO_2) will drop from normal (>85 mmHg). Similarily, if there is an increased pulmonary blood flow to a normally ventilated area of lung, e.g., the lung apex in the supine position, the PaO_2 will drop.

A single arterial blood sample was taken from all patients while recumbent and prior to recording a spirogram. The pH, carbon dioxide content, oxygen content and capacity were determined, and from those values the carbon dioxide tension, oxygen saturation and oxygen tension were calculated. Arterial oxygen saturation was reported since the oxygen electrodes for measuring oxygen tension were not in use in our laboratory at the time of the initial studies. In recent evaluations, the oxygen and carbon dioxide tensions of arterial blood were measured directly.

The angle of the curvature, vital capacity maximum breathing capacity, and arterial oxygen saturation or arterial oxygen tension were determined prior to surgery, two weeks after surgery, six months after surgery, and one, two, and five years after surgery whenever possible.

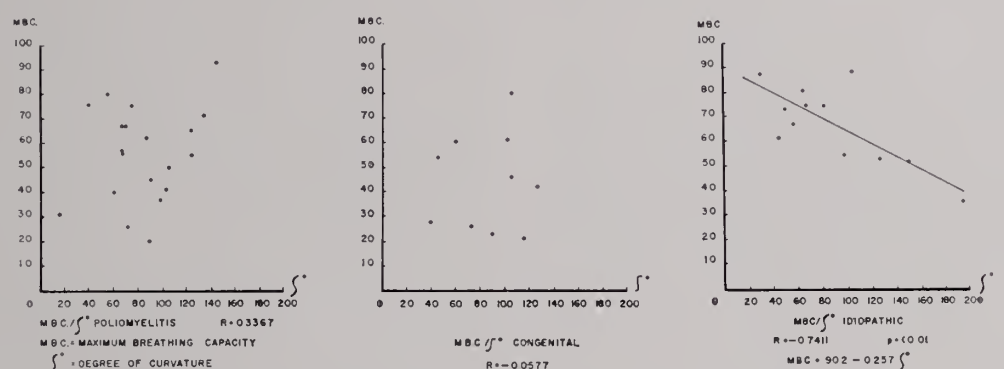


Fig. 2—Maximum breathing capacity as a percentage of normal is compared to the degree of curvature in thoracic scoliosis: (a) secondary to poliomyelitis, (b) of a congenital nature, (c) idiopathic in nature, and the significant correlation is shown in the idiopathic group.

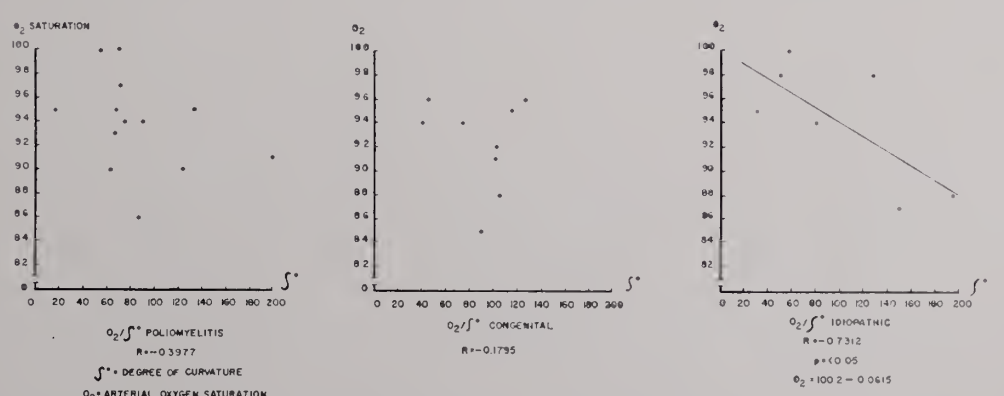


Fig. 3—Arterial oxygen saturation as a percentage of normal is compared to the degree of curvature in thoracic scoliosis: (a) secondary to poliomyelitis, (b) of a congenital nature, (c) idiopathic in nature and the significant correlation is shown in the idiopathic group.

Results

Though all patients showed a tendency towards an increased respiratory rate and a smaller tidal volume than normal, these changes were not statistically significant, and minute volume and alveolar minute ventilation were within the normal range preoperatively and postoperatively.

Cough was within what we believe to be the normal range with respect to both volume and flow rate in all patients except those who had tracheotomies preoperatively. Both flow and volume, but primarily flow, were significantly lower in the poliomyelitis group. No postoperative spirographic assessment of a cough was made.

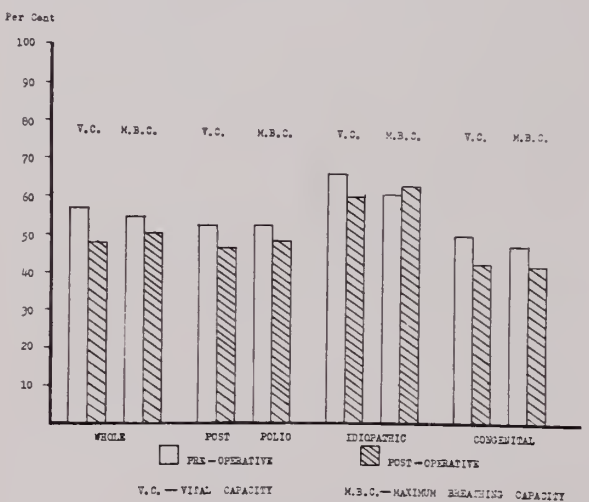


Fig. 4—Preoperative and postoperative comparison of vital capacity and maximum breathing capacity both as a percentage of normal, in 31 patients one year after thoracic scoliosis correction by the Harrington method. The group as a whole is compared and a separate comparison in the three sub-groups is made.

Degree of Spinal Curvature

The angle of the preoperative thoracic curvature ranged from 40 to 180 degrees with an average curve of 87 degrees. Two years after surgery, the average curve was 53 degrees and five years after surgery, the average curve remained the same.

The severity of the curvature of the spine was correlated with vital capacity, maximum breathing capacity (both expressed as a percentage of a predicted normal) and with arterial oxygen saturation in the three etiological groups.

Vital Capacity

In comparing the vital capacity (Figure 1a, b, c) with the degree of spinal curvature, there is no significant correlation between these values in the congenital or polio group. If the lone point in Figure 1b is dropped, then a significant correlation is being approached. There is a significant negative correlation between the vital capacity and degree of spinal curvature in the idiopathic group. (The greater the spinal curvature, the less the vital capacity and vice versa; $R = -0.8145$, $P = <0.005$).

There was a positive correlation between the vital capacity and the maximum breathing capacity (each expressed as a percentage of a predicted normal) both before operation ($R = 0.69195$, $P = <0.005$) and two years afterward ($R = 0.8016$, $P = <0.01$). For 31 patients, the average vital capacity one year after

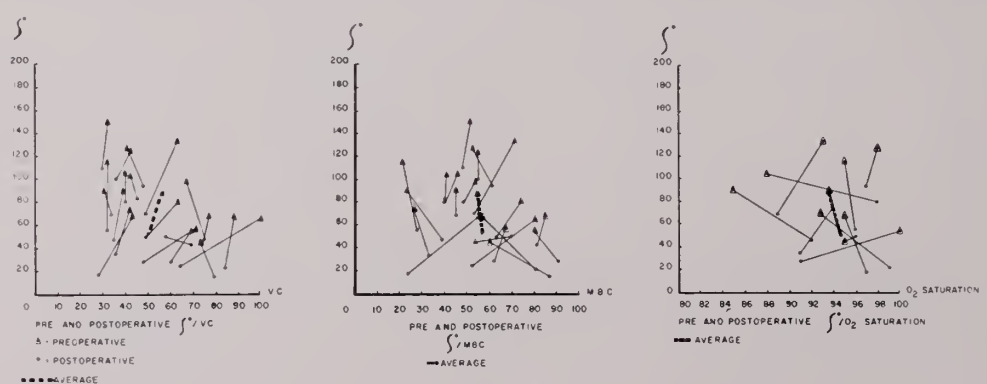


Fig. 5—The degree of curvature is compared with: (a) vital capacity, (b) maximum breathing capacity, and (c) arterial oxygen saturation, preoperatively and two years postoperatively.

operation decreased significantly from 57 percent of the predicted value to 48 percent. In the poliomyelitis group the vital capacity decreased from 52 to 48 percent; the congenital group showed a decrease from 51 to 43 percent, and the values in the idiopathic group decreased from 67 to 61 percent (Figure 4). Two years after surgery the results were similar (Figure 5a); in 27 patients studied five years after surgery values were unchanged.

There is no correlation in the change in angulation following surgery with the decrease in vital capacity and maximum breathing capacity except in the poliomyelitis group (seven patients), in which there appeared to be a significant positive correlation between the change in the angle of the curvature and the vital capacity ($P = <0.025$, $R = 0.77833$); the more the spinal curve decreased, the greater the decrease in vital capacity (Figure 6). However, the sample analyzed was small and the level of significance is therefore not high.

Maximum Breathing Capacity

Maximum breathing capacity similar to vital capacity showed a significant negative correlation with the curvature in the idiopathic group ($R = -0.7411$, $P = <0.01$) but no significant correlation in the congenital and poliomyelitis groups (Figure 2a, b, c).

One year after surgery the preoperative maximum breathing capacity of the group as a whole had decreased from 55 to 51 percent of the predicted value. In the poliomyelitis group, the decrease followed the same pattern (52 to 49 percent); and the decrease was of a greater magnitude in the congenital group (48 to 41 percent). In the idiopathic group, on the other hand, the maximum breathing capacity increased from 61 to 64 percent (Figure 4).

Two years after surgery the preoperative and postoperative values were the same, 55 and 56 percent of predicted. Values in 23 patients after five years were also the same.

Arterial Blood Oxygen Saturation

Arterial oxygen saturation showed a negative correlation with the curvature in the idiopathic group and, like vital capacity and maximum breathing capacity, no correlation in the congenital and postpoliomyelitis groups. The negative correlation with the curvature in the idiopathic groups showed the lowest level of significance of the three groups, presumably because of the small sample ($R = -0.7312$, $P = <0.05$) (Figure 3a, b, c).

Two years after surgery the oxygen saturation improved from a preoperative value of 93.5 percent (median 93 to 94 percent group) to a postoperative value of 95.2 percent (median 95 to 96 percent group), a physiologically and statistically significant improvement. Values in 23 patients five years after surgery were not significantly different from the values obtained at two years.

Tracheotomy

Fifteen of 75 patients required tracheotomy. On 12, this was done as an elective preoperative operation on the basis of a poor cough, a vital capacity and maximum breathing capacity below 35 percent of predicted, or the probable

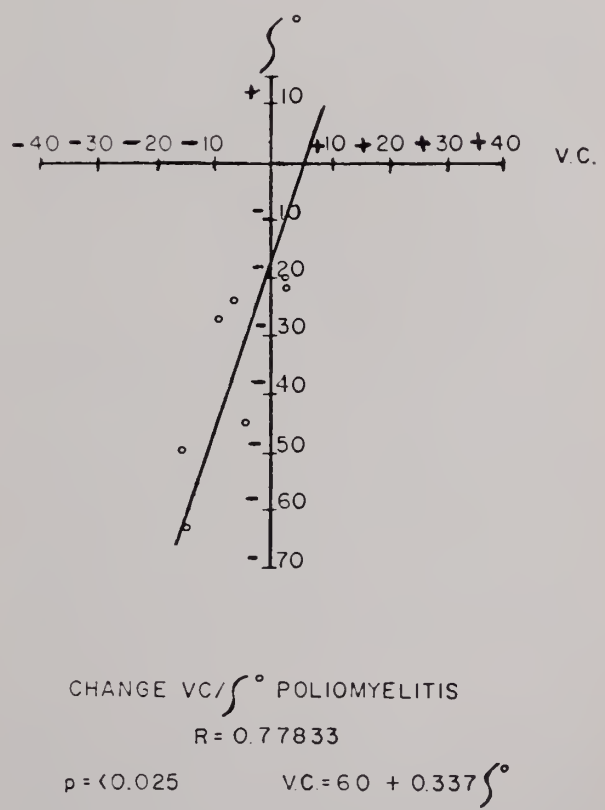


Fig. 6—The correlation is shown between the reduction in the spinal curvature following surgery and the decrease in vital capacity as a percent of the preoperative predicted value in patients with thoracic scoliosis secondary to poliomyelitis.

need for postoperative respiratory assistance. At the present time we do not perform routine tracheotomies but will provide postoperative assisted ventilation using a naso-tracheal tube. Of these 12 patients, scoliosis was secondary to poliomyelitis in seven, idiopathic in nature in one, and congenital in four. Postoperatively, three additional patients required tracheotomies and assisted ventilation. Two of these had had poliomyelitis and one, congenital scoliosis. One of these patients developed pneumonia postoperatively, one became comatose because of water intoxication, and the third went into cardiopulmonary failure.

Discussion

Mechanics

One would not expect a correlation to exist between the degree of spinal curvature and the vital capacity or maximum breathing capacity in either the poliomyelitis group or the congenital scoliosis group. In the poliomyelitis group the scoliosis is secondary to muscle weakness either overt or masked. The decrease in lung volumes and air flow through the tracheobronchial tree is influenced by this muscle weakness. Similarly, congenital scoliosis is frequently seen with concomitant neuromuscular diseases and other congenital intracardiac defects which would influence both vital capacity and maximum breathing capacity independent of the effects of the scoliosis.

Idiopathic scoliosis occurs with muscle imbalance only; thus the major factor affecting pulmonary function in patients with idiopathic scoliosis is the decrease in size of the thoracic cavities which have been distorted by the twisted vertebral column. Therefore it would be expected that there would be a significant correlation between the degree of curvature and the vital capacity, the maximum breathing capacity or both in patients with idiopathic scoliosis.

*One patient had a very marked decrease in vital capacity one year after surgery and at re-operation showed complete immobilization of the rib cage on one side secondary to inadvertent fusion of the transverse processes and costovertebral joints (Table 1). Following removal of the fusion mass between the ribs and transverse processes his vital capacity increased from 39 to 54 percent of the predicted value. This patient and one other, in whom the vital capacity was decreased similarly 18 months after surgery, were withdrawn from the postoperative comparative group since their decreases in vital capacity were secondary to complications and not to the surgical procedure itself.

Vital Capacity

The reason for the decrease in vital capacity after fusion is not evident from these studies. The possibility exists that interference with rib motion after surgery is a cause of the decreased vital capacity.* Another possibility is that straightening of the curve decreases the volume of the hemithorax lying on the concave side of the vertebral curve which is usually the larger lung.[21,22] Postoperatively the ribs on this side come closer together and form a more acute angle with the vertebral column. One would not expect as large an overall decrease in vital capacity in patients with idiopathic scoliosis as in those whose deformity was secondary to poliomyelitis, because the lungs in the former group are anatomically normal and the lung on the convex side of the curve can compensate to some extent. Such a response is shown in Table 2 where the preoperative and postoperative values of a 16-year-old girl with idiopathic scoliosis are compared. In patients whose curve is the result of poliomyelitis, however, the lung in the hemithorax adjacent to the convexity of the curve when seen at autopsy is small and infantile (medial arteriolar muscular hypertrophy, smaller capillary bed and less distensible), and frequently contains atelectatic areas. As a result the lung has a very low compliance; thus, it is unable to compensate for the postoperative decrease in volume. This observation may also account for the significant positive correlation that appears to exist between the amount of correction of the curvature and the decrease in vital capacity in the poliomyelitis group.

Arterial Oxygen Desaturation

Arterial oxygen desaturation has been attributed to alveolar hypoventilation. Since there was no hypercapnia in any of our patients, alveolar hypoventilation cannot account for the arterial desaturation seen in them. Mild arterial oxygen desaturation (92 percent to 95 percent saturation) can be corrected in most cases by minimum exercise or hyperventilation with room air, indicating that poor air distribution is the cause of this mild desaturation. More severe arterial desaturation (88 percent to 91 percent saturation) cannot be corrected

TABLE 1

The effects of an inadvertent fusion of the transverse processes and costovertebral joints on the pulmonary function of an 18-year-old male with a post-poliomyelitis thoracic scoliosis

	Preoperative Harrington Procedure	One Year After the Harrington Procedure with Inadvertent Costo-vertebral Joint Fusion	One Month After Removing the Fusion Mass
Vital Capacity (cc)	1575 (42%*)	575 (15%*)	750 (20%*)
Maximum Breathing Capacity (L/min.)	50 (53%*)	18 (19%*)	45 (48%*)
PaO_2 (mm Hg)	90.0	54	83
Oxygen Saturation (per cent)	96.2	86.2	95.3
$PaCO_2$ (mm Hg)	41.8	77	55.8

*Percentage of predicted.

TABLE 2

The effects on the pulmonary function of a 17-year-old girl who had a Harrington procedure to correct an idiopathic thoracic scoliosis

	Preoperative Harrington Procedure	Six Months Postoperative
Vital Capacity (cc)	1750 (55%*)	1800 (56%*)
Maximum Breathing Capacity (L/min.)	50 (54%*)	50 (54%*)
Angle of Thoracic Curve	82°	47°
PaO_2 (mm Hg)	72	90
Oxygen Saturation (per cent)	93.7	96.2
$PaCO_2$ (mm Hg)	37.0	40.0

*Percentage of predicted.

TABLE 3

The improvement in the pulmonary function of a 26-year-old female with a post-poliomyelitis thoracic scoliosis and alveolorespiratory failure is shown following halo-femoral traction. The improvement in vital capacity and $PaCO_2$ is maintained and the improvement in PaO_2 and maximum breathing capacity continue following a Harrington procedure

	Pre-Treatment	Following Three Weeks of Halo-Femoral Traction Preoperative	Two Months After a Harrington Procedure	Six Months After a Harrington Procedure
Vital Capacity (cc)	600 (24%*)	825 (33%*)	760 (31%*)	800 (32%*)
Maximum Breathing Capacity (L/min.)	18 (30%*)	23 (38%*)	23 (38%*)	27 (45%*)
PaO_2 (mm Hg)	69	65	74	84
Oxygen Saturation (per cent)	91.3	91.3	94.5	95.6
$PaCO_2$	46.5	41.0	44.0	42.0

*Percentage of predicted.

by mild exercise or by breathing oxygen concentrations greater than 20 percent. These results, as well as the presence of normal CO diffusing capacities in patients with scoliosis, show that an alveolar capillary block to oxygen is not the cause of the arterial desaturation.

The mild desturation most commonly seen in idiopathic scoliosis is probably the result of uneven pulmonary ventilation caused by collapse of a greater than normal number of alveoli when the lung is in a resting midposition. Thus when the lung is maximally expanded during hyperventilation or exercise, the ventilation becomes even and arterial saturation normal. The more severe arterial desaturation may be in part the result of uneven ventilation, but probably to a considerable extent the result of a veno-arterial shunt and altered regional perfusion.[13,21] Two major causes of such shunting can be suggested. As noted previously, the lung adjacent to the convexity of the curve has been shown to be small and infantile, frequently containing large atelectatic areas. Blood, perfusing these unventilated areas, returns to the left auricle desaturated and decreases the saturation of the peripheral arterial blood. An increase in pulmonary vascular resistance may also cause an increased shunting of blood around the alveolar capillary bed through pre-capillary channels.

Altered ventilation/perfusion ratios have been shown to occur in the convex lung with a resultant decrease in arterial oxygen tension. A more uniform perfusion of the convex lung rather than the preferential perfusion of the dependent portion of the lung occurs and, because ventilation to these areas was normal or reduced, blood passing through the capillary bed was inadequately oxygenated.[21] This type of arterial desaturation was more commonly seen in patients with scoliosis due to poliomyelitis and in those with severe idiopathic scoliosis. Patients with scoliosis usually die of right heart failure secondary to cor pulmonale which in turn is secondary to an increased pulmonary vascular resistance. What effect does a mild hypoxemia have on the pulmonary vascular bed? Does correcting the spinal curvature reduce the probability of future pulmonary hypertension by correcting the mild arterial desaturation or by preventing the development of a greater degree of desaturation? After operation the arterial oxygen desaturation is less (Table 3), but there are too few cases to carry out a satisfactory statistical analysis; only long follow-up observations with serial studies of pulmonary hemodynamics before and after surgery will supply answers.

Prime[12] could find only two cases of kyphoscoliosis in 34, where any evidence of obstruction to airflow was present. There were two cases in our series of 74 that showed a significant degree of airway obstruction preoperatively. In both cases there was a significant objective improvement postoperatively in the one-second timed vital capacity, maximum expiratory flow rate, and maximum breathing capacity. Subjectively there was marked improvement in one patient; she "no longer wheezed at night or when she got a cold, and now she could cough from the bottom of her chest." Abrahamson[24] has provided anatomical evidence of kinking of pulmonary vessels and of the tracheobronchial tree in kyphoscoliosis, and it may well be that surgery in these two patients corrected this abnormality. With the use of xenon[133] minor degrees of airway obstruction have been demonstrated in patients with scoliosis, and in most cases the slowed flow rates were unilateral and occurred in the convex lung.[13,21,23]

This study analyzed the effects of a particular surgical technique on three parameters of lung function only. Many other aspects of pulmonary function such as changes in lung and chest wall compliance, residual volume, physiological deadspace and the work of breathing were not taken into account. Probably most important of all, our study did not evaluate pulmonary hemodynamic changes or any central cardiovascular changes. Because of these limitations, our findings cannot be used alone to judge the effect of this particular surgical technique. They should only form a basis for comparison with the results of other forms of treatment. Cook,[10] in a small number of patients with scoliosis seen before and after spinal fusion, noted a decrease in lung volumes after fusion. It would therefore appear that the decrease in vital capacity may follow any surgical correction and certainly is present while a patient is in a body cast.

Conclusions

In 74 patients with thoracic scoliosis examined before surgery there was a significant negative correlation between the angle of the curvature and the vital capacity, maximum breathing capacity and arterial oxygen saturation in the idiopathic group (24 patients). No such negative correlation was found in the poliomyelitis group (31 patients) or in the congenital group (13 patients).

Values at two and five years after surgery were similar to those obtained at one year when vital capacity was decreased from 57 to 48 percent of predicted; and maximum breathing capacity was decreased from 55 to 51 percent of predicted. Arterial oxygen saturation improved significantly from 93.5 to 95.2 percent after operation and the spinal curvature decreased from 87 to 53 degrees.

The Harrington method for the correction of thoracic scoliosis did not improve the average vital capacity or maximum breathing capacity but did improve the overall ventilation/perfusion ratio in this group of patients. However, in individual patients, all three measurements may be improved postoperatively.

Since there is a positive correlation between the decrease in the spinal curvature and the decrease in vital capacity in the poliomyelitis group, over-enthusiastic correction of the curve of such patients is to be avoided; but treatment should be instituted as soon as a curve is noted in order to preserve what lung function is left.

Before operation there was a correlation between the amount of curvature and the decrease in vital capacity in the idiopathic group; therefore treatment of idiopathic scoliosis should be instituted if there is any sudden increase in the curvature or as early as possible if the curve is slowly progressing. Treatment then will preserve what respiratory function is present at the time of surgery.

The primary aim of treatment should be restoration or preservation of function and not anatomical perfection alone.

Summary

Neither vital capacity nor maximum breathing capacity is improved in scoliotic patients treated by the Harrington rod method. Ventilation/perfusion ratios are improved, however, as indicated by a clinically and statistically significant improvement in the arterial oxygen saturation and oxygen tension.

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A mule has neither pride of ancestry nor hope of posterity.—Ingersoll

Historic Hospitals



Rahere's Well at the foot of the Altar of St. Bartholomew's Basilica, Isola Tiberina, Rome.

Few of the world's hospitals are older or can point to more distinguished medical staffs than St. Bartholomew's Hospital of London. Certainly none can boast of a more exotic beginning.

In the early twelfth century the English cleric and courtier, Rahere, was stricken with malaria while on pilgrimage in Rome. He is said to have resorted to the island in the Tiber which at that time was already a medical center of some twelve centuries' standing. His treatment on the island included water from the well shown in this photograph and thought since the days of the ancient Romans to be curative. In the background is the Altar of the Basilica of St. Bartholomew which was built around the well about 1100 A.D.

During Rahere's illness the Apostle St. Bartholomew appeared to the suffering Englishman and ordered him to build a church and hospital on his return home. Showing an amazing knowledge of English geography for a Galilean, St. Bartholomew specified a site in the London suburb of Smithfield.

On his return to England Rahere persuaded the Bishop of London to intercede with the king, who provided the site in Smithfield where the hospital dedicated to St. Bartholomew still stands. The founding of the hospital occurred in the year 1123. The original structures were probably scattered one-storied wooden buildings of which there remains no trace.

Rahere himself joined in the treatment of the patients, which in the early years was largely faith-healing in the name of St. Bartholomew. Thus are linked the histories of England's most venerable hospital and one of the oldest medical sites in Rome.

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Long-Term Effects of Diskography in Dogs

JAMES G. GARRICK, M.D.* and C. ROGER SULLIVAN, M.D.†

One criticism of diskography has been a questioning of the value of the procedure as a diagnostic technique (Holt 1964). The literature contains many isolated accounts of disk abnormalities possibly resulting from inadvertent mechanical violation of the integrity of the disk during diagnostic lumbar puncture, spinal anesthesia, and intrathecal injections of medications (Everett 1941, Gardner et al. 1952, Gellman 1940, Milward and Grout 1936, Pease 1935, Raaf 1941). In spite of these reports, there has been no question raised regarding the impunity of puncturing the annulus fibrosus and injecting a foreign substance into the nucleus pulposus.

Many authors suggest that the chemistry, physiology, and hydrodynamics of the intervertebral disk are such that the introduction of any foreign material could easily cause significant changes (Hendry 1958, Inman and Saunders 1947, Keyes and Compere 1932, Naylor 1962). The only experimental evidence to the contrary was reported by Lindblom (1951), who performed diskography on the disks of dogs' tails and found no ill effects. However, there seem to be significant differences between the non-disease-susceptible tail disks of dogs and the disease-susceptible cervical and lumbar disks of man. Therefore, it seemed justifiable to attempt to determine the presence and magnitude of change occurring in a normal disk after diskography.

Methods

Thirty-one mongrel dogs of random sex and age distribution were used. Because clinically evident disk protrusion is seen in dogs, usually between the thirteenth thoracic and third lumbar disks (Olsson 1951), these were the levels chosen for diskography which was performed 54 times as previously described (Garrick and Sullivan 1964).

Roentgenograms of the spinal column were obtained during the procedure and at six months and one year afterward. During the follow-up period, all animals were observed for clinical signs of disk disease. At one year after diskography, each animal was killed; the spinal column from T11 to L5 was removed en bloc, cleaned of soft tissue, sectioned in a midsagittal plane, and examined grossly. After one week of fixation in 10% formalin solution, a 5-mm sagittal section was made and decalcified.

After complete decalcification, sections were cut to contain the disks and the adjacent vertebral bony end plates. These were embedded, sectioned sagittally at a thickness of 5μ, and stained by the standard hematoxylin and eosin method.

All sections (those of disks subjected to diskography and of normal disks) were examined in a random-blind fashion by one of us (J.G.G.) and by Dr. D. C. Dahlin, Section of Surgical Pathology, Mayo Clinic. The criteria for canine disk abnormalities were those presented by Hansen (1951) and Olsson (1951).

Results

All animals recovered from the procedure without any clinical evidence of disk abnormalities. Grossly, roentgenographically, and microscopically there was no evidence of any abnormalities of the disks or of adjacent bony structures. There was also no evidence of disk space infection in any of the animals.

Discussion

No attempt was made during the course of the study to minimize possible changes in disks secondary to the procedure. Disks at levels most likely to undergo degenerative changes

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were chosen for diskography, and the subsequent activity of the animals was not limited in any way.

The only deviation from diskography as it is performed on human patients was puncture of the annulus at the posterolateral aspect rather than directly posterior. This was necessitated by the configuration of the posterior elements of the canine spinal column.

Summary

Fifty-four diskograms were made on 31 dogs by techniques paralleling those used in human diskography. Roentgenograms taken six and 12 months postoperatively as well as gross and microscopic examination of the disks at 12 months postoperatively failed to reveal any deviation from normal.

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In 1964, at San Francisco, he received a First Award for a modern oil painting at the American Medical Association's Physician's Art Show and most recently has begun watercolor painting. His inspiration for "Hawaiian Sunset" originated while Dr. Lee was convalescing.

My good friends, while I do most earnestly recommend you to take care of your health and safety, as things most precious to us, I would not have that care degenerate into an effeminate and over-curious attention, which is always disgraceful to a man's self, and often troublesome to others.—Edmund Burke

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No one becomes wise who is sure he already is. —Herbert Prochnow

Sporotrichosis

A Report of 21 Cases

FREDERIC T. BECKER, M.D.* and HADLEY R. YOUNG, M.D.†

SPOROTRICHOSIS HAS occurred sporadically in nurserymen, especially in the Mississippi River Valley area, and is usually associated with contact with sphagnum (peat bog) moss. We have recently treated eight patients having this disease, and 13 others similarly afflicted have been observed by physicians in this area. Sporotrichosis was proved by culture in all of these patients and all had had contact with sphagnum moss which also harbored the fungus *Sporotrichum schenckii*.

In 1926 H. Foerster[1] concluded that sporotrichosis was an occupational disease in people working with plants and that the Mississippi River basin was an endemic area for this fungus. In 1941 Gastineau[2] et al. reviewed the literature through 1940 and confirmed Foerster's observation of the high prevalence of this disease in agricultural and forestry workers. They also found that 67 per cent of 205 reported cases occurred in the Mississippi River basin. Sphagnum (peat bog) moss was one of the few materials used by all the patients and the organism was frequently recovered in this moss. More recently D. J. D'Alessio[3] et al. reported 14 cases of sporotrichosis occurring in a state tree nursery in Vermont, where the moss, which was proved to be the source of the infection, was obtained from the state of Wisconsin. E. Shockett[4] et al. reported four cases from the state of Florida in nurserymen, all of whom had contact with moss; here again, the material had been obtained from the state of Wisconsin.

Case History

In May 1968, a 37-year-old white male obtained trees, packed in sphagnum moss and shavings, from a local nursery. While planting these trees a blister appeared on the dorsal surface of his left hand, and several weeks later chills and fever developed along with red streaks up his left forearm. His local physician treated him with antibiotics and hot compresses. His condition improved, only to recur one month later; on this occasion antibiotics and hot compresses were again employed. The appearance of 12 reddened nodules scattered up the left forearm caused the patient to consult another physician on July 3, 1968. Further wet compresses and elevation were used for three weeks without benefit; then the patient was referred to one of us (FTB).

Our examination in late July disclosed a healed scar at the site of the previous ulcer on the dorsal surface of the left hand; and scattered up the anterior surface of the left forearm were a dozen erythematous nodules varying from 2 to 5 cm. in diameter (Figure). Some were indurated and others fluctuant and ulcerated. No regional adenopathy was palpable and the patient was afebrile. Hemoglobin, white blood count and differential white cell count, urinalysis and the erythrocyte sedimentation rate were normal. A 4-mm. punch biopsy was made of one of the fluctuant nodules, releasing an ounce of purulent



Figure—Healed scar on dorsum of left hand with nodular and ulcerated lymphangitis typical of sporotrichosis.

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†Duluth, Minnesota.

material, which was cultured on blood and mycosel agar. A week later a yeast-like organism was identified as Sporotrichum schenckii. Later pathogenic studies on animals confirmed this diagnosis. Pathologic examination revealed a chronic inflammatory process with the presence of numerous foreign body giant cells deep in the dermis. Acid-fast, Hotchkiss and McManus and the special stains described by B. F. Fetter[5] et al. for demonstrating the Sporotrichum schenckii organism, were negative.

A saturated solution of potassium iodide was prescribed in a dosage of 10 drops three times a day, increasing one drop with each dose until a daily total dose of 100 drops was maintained for three months. The patient was last seen on September 17, 1968, at which time the lesions were healed and he was advised to continue potassium iodide solution, 10 drops three times a day, for another month. Outside of a scattered, papulopustular eruption which developed around his neck, there were no complications.

On August 10, 1968, we visited the tree nursery and made cultures from all of the various storage bins of sphagnum moss and the mixture of moss and shavings used in packing the 1968 trees. Positive identification of Sporotrichum was obtained from the 1968 shavings and moss mixture, and likewise from moss purchased in 1967, which was utilized in 1968 tree packing. We also learned at the tree nursery that 13 of the itinerant workers who were engaged in packing trees with the sphagnum moss mixture had become ill, and their physicians and dermatologic consultants had diagnosed sporotrichosis in each case. Lesions similar to those of the others had developed in three additional workers, but they had not consulted physicians.

Summary of Our Additional Seven Cases

Seven other patients were observed by us and all gave a history similar to that described in the preceding case summary. They were handling and planting trees and, following trauma, cutaneous ulcers with ascending nodular and fluctuant lymphangitis had developed. The etiologic organism was proved culturally to be sporotrichosis. Treatment was with oral potassium iodide, which produced clinical improvement within 30 to 60 days. Evidence of myocardial infarction was documented ten days after the potassium iodide therapy in two of the patients, one of whom expired; but the other made an uneventful recovery and potassium iodide therapy was resumed without any further untoward reaction.

Clinical Characteristics

Sporotrichosis has been divided into six different clinical types by de Beurmann and Gougerot:[6] (1) lymphatic, (2) epidermal, (3) disseminated, (4) mucosal, (5) skeletal, and (6) visceral. The first two types are the most common, making up 75 per cent of all reported cases, and this paper will be limited to these two types.

The patient usually gives a history of handling trees or other plants which have been packed in sphagnum moss for transportation. He frequently suffers minor trauma to the skin, after which an indolent ulcer develops. Quite commonly, several weeks later, this is followed by an ascending lymphangitis with multiple subcutaneous nodules appearing along the involved lymphatics. These nodular lesions become fluctuant and may ulcerate. Associated regional lymphadenopathy is unusual. Diagnosis can be made by history, clinical observation and culture on special media for fungi. The organism is difficult to demonstrate by fresh tissue preparations or by the usual histologic methods.

Differential Diagnosis

When confronted with a patient having a solitary ulcerated granulomatous lesion, the differential diagnoses must include primary tuberculosis and swimming-pool granulomas. (A detailed review of the differential characteristics of these entities is made by Adams, Robert[7] et al.). Also to be considered are deep fungal infections such as coccidioidomycosis, histoplasmosis, nocardiosis, chromoblastomycosis and blastomycosis. The primary chancre of syphilis, neoplasms, tularemia, anthrax and other pyodermic infections should also be borne in mind. The unique feature of sporotrichosis is the development, along the course of lymphatics, of nodules which occasionally ulcerate. The best confirmation of the diagnosis of sporotrichosis is by culture. The organism grows readily on Mycosel medium and can be identified in seven to 10 days. Unfortunately diagnosis from microscopic sections and tissue smears has been unrewarding.

Therapy

Potassium iodide is the treatment of choice for sporotrichosis of the localized form; it apparently is ineffective in the disseminate form of this disease due to immunological factors as yet unexplained. The usual dosage is ten

drops of saturated solution of potassium iodide three times daily in water or milk, increasing by one drop daily to 30 or 40 drops three times daily. General improvement is noted in one week after initiation of this treatment, and therapy may be discontinued in most cases four to six weeks after clinical resolution of the lesions is apparent. Gastrointestinal intolerance may be circumvented by the administration of sodium iodide intravenously instead of oral potassium iodide. A 10-per cent solution of sodium iodide is administrated intravenously and slowly, beginning with 25 cc and increasing by 5cc with each injection to a maximum dose of 100 cc. This is given five times a week for a period of four to six weeks or until complete healing occurs and then continued one to two weeks thereafter. Other side effects of iodide therapy may include photophobia, conjunctivitis, salivary gland swelling, anaphylaxis, polymorphous light eruption, acne, iododerma, and pustular psoriasis. Most side effects can be eliminated by reducing the dosage.

According to Urabe[8] et al. Sporotrichum schenckii is dimorphic, with the most infectious yeast phase being present in vivo. They have shown that potassium iodide is fungicidal in its molecular form at concentrations in tissue as low as 1:10,000 when the organism is present in the yeast phase. The usual oral method of potassium iodide administration, as described, produced a concentration in most individuals of 1:8,000 in the body tissues.

Despite its toxicity, amphotericin B is a good alternative in potassium-iodide-sensitive individuals and may be indicated in the systemic form. Griseofulvin has been reported as variably successful in the treatment of the localized form of sporotrichosis. Superficial x-ray therapy has been utilized in the treatment of the granulation tissue. Surgical excision has been attempted, but it is contraindicated except for aspiration. Administration of a vaccine prepared from the yeast phase has certain proponents but is not widely used. Hot compresses have been employed when the condition is localized to an extremity, the rationale being that the yeast form grows poorly at above 38 degrees centigrade. Both penicillin and streptomycin have been reported as promoting the growth of Sporotrichum schenckii.

Comment

All eight of our patients responded in the usual manner to potassium iodide therapy, but myocardial infarction developed in two patients. Review of the world literature does not reveal any reports of myocardial infarction as a consequence of or incidental to the use of iodides. The relationship of iodides to precipitation of myocardial infarction would, therefore, seem to be merely speculative at this time.

Summary

The authors observed eight patients in whom sporotrichosis was proved by culture; in two of these, diagnoses were further confirmed by animal inoculations and pathogenic studies. Thirteen other patients observed by local physicians all proved culturally to have sporotrichosis and were treated with potassium iodide, resulting in resolution of their disease without any complications except the two unusual instances of myocardial infarction.

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Happiness and misery are not fated but self-sought.—Cul'nary Almanac.

Five Score and More

Centenarians

In the face of the Biblical stipulation of three score and ten, centenarianism is a phenomenal achievement that arrests attention, piques curiosity, and sometimes commands awe. When we hear of an individual attaining his hundredth birthday we almost invariably ask: How did he do it? As if it were a wholly voluntary act on his part!

Doubtless most centenarians entered life carrying the happy genes for longevity and endowed with fundamentally sound constitutions. But those two factors alone by no means assure a centennial. Only by a perceptive look into the lives of some paragons who lived to a venerable five score and a bit more can we derive a fuller answer to the question: How did he do it?

Britannia was the motherland of several renowned figures who numbered their years in three instead of only two digits. There was the Irish prelate, **Bishop John Leslie** (1571-1671), articulate and active militant both ecclesiastically and politically—all in the name of God and the King. Though a churchman he presumed, in the fervor of his convictions, to lead troops into battle. Assuming generalship on one occasion, yet a bit dubious either of his cause or of his divine prerogative, he offered up the following ambivalent prayer just preceding the military engagement with the enemy: "Though then Thou vouchsafest not to be with us, be not against us, but stand neuter this day, and let the arm of the flesh decide it." And the arm of the flesh did decide it on that occasion; God's intervention was not evident.

"How *long* I shall live is only in God's power, but it is in my power *how well.*" These sage and succinct words were spoken by **Diplomatist Richard Bulstrode** (1610-1711), distinguished British Royalist, Plenipotentiary at the Court of Brussels, and Knight. Also a philosopher and prolific author in both English and Latin. Physically and mentally his buoyancy and vigor never perceptibly diminished. Even as an octogenarian he was still able to walk twelve miles a day; and who knows how much longer he might have graced the English landscape had not an attack of acute indigestion carried him off at age 100.

Martin Routh, Scholar, prominent Academician, and President of Magdalen College for sixty years, lived from 1755 to 1854, departing this life just short of the century mark. Nevertheless we include him here since at 94 he proved his physical stamina by walking six miles on a rough road under a scorching sun with no dire results, and demonstrated his mental proficiency at 99 by authoring a learned treatise. Once, when disabled in his nineties by a ponderous tome falling on his foot and advised by his doctor to go to bed, he replied: "No, thank you, sir, no, thank you. If you once get me into bed, I know you will never get me out again."

Philanthropist Moses Montefiore's life spanned the century from 1784 to 1885. Self-appointed crusader for the amelioration of the lot of oppressed and persecuted Jewish minorities in Europe, Asia Minor, and Northern Africa, he traveled about constantly from one critical area to another under physically strenuous, even politically dangerous conditions. At age 89, having learned of a premature report of his own death, he said: "Thank God to have been able to hear of the rumor, and read an account of the same with my own eyes, with-

(Continued to page 874)



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Dosage and Administration: *In the Female.* One 250-mg. tablet orally three times daily for ten days. Courses may be repeated if required in especially stubborn cases; in such patients an interval of four to six weeks between courses and total and differential leukocyte counts before, during and after treatment are recommended. Vaginal inserts of 500 mg. are available for use, particularly in stubborn cases. *When the vaginal inserts are used* one 500-mg. insert is placed high in the vaginal vault each day for ten days and the oral dosage is reduced to two 250-mg. tablets daily during the ten-day course of treatment. Do not use the vaginal inserts as the sole form of therapy. *In the Male.* Prescribe Flagyl only when trichomonads are demonstrated in the urogenital tract, one 250-mg. tablet two times daily for ten days. Flagyl should be taken by both partners over the same ten-day period when it is prescribed for the male in conjunction with the treatment of his female partner.

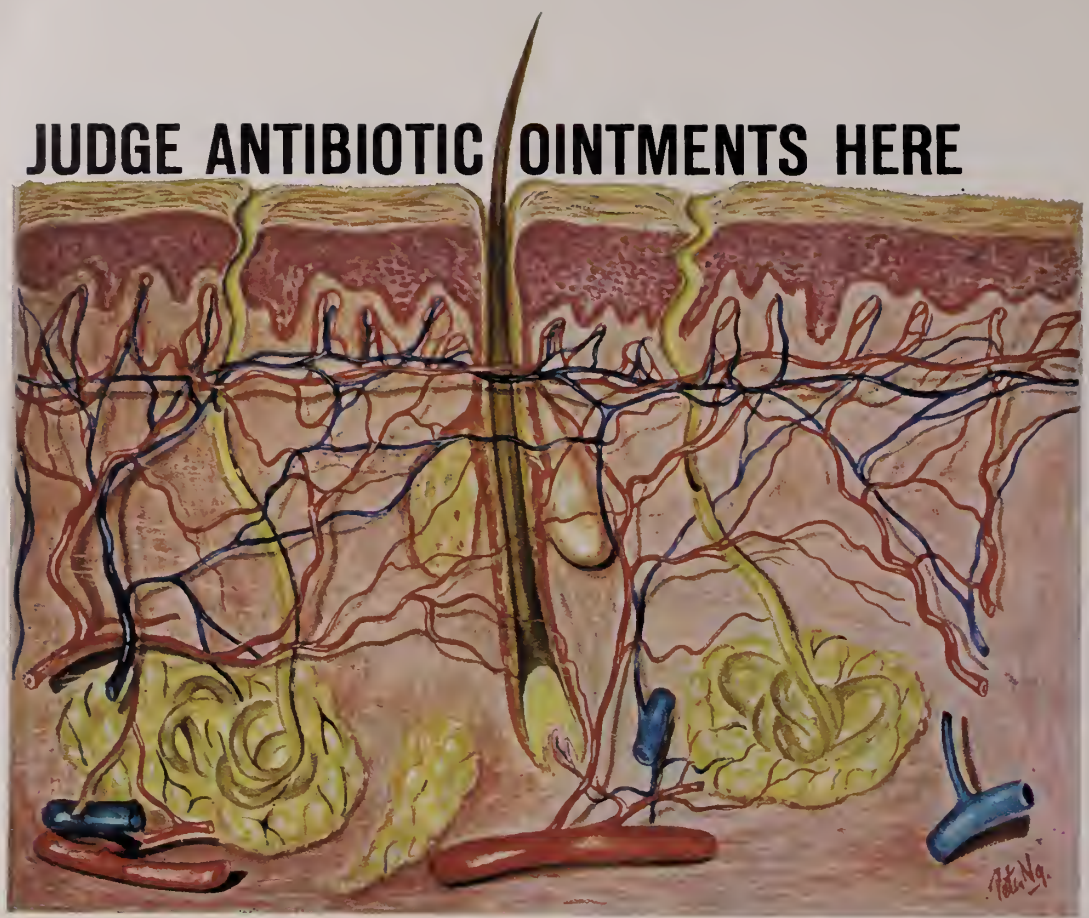
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Editorials

Pathology in Vietnam

IN PART DUE to twenty years of devastating wars, continuous overpopulation and Caucasian colonization of many decades, the South Vietnamese are indeed an underdeveloped nation. On the other hand, there is no question as to their mental acuity, ambition, interest in and capacity for advancement. What is needed is a continuation of generous and humanitarian efforts by the people of the United States through their Agency For International Development (USAID).

The French overseers willingly taught the Vietnamese medicine but neglected some of the other means of improving their existence. Thus there are some one thousand native physicians, of whom two thirds are in the armed forces. So it is little wonder that the great void in medical care of the fifteen million population has permitted six thousand Chinese witch doctors to flourish and even receive some legal recognition. With the political successes of our chiropractors, our country fails to set much of an example!

The faults of the teacher are evident in the student. The department of Acupuncture in The Faculty Of Medicine Of Paris teaches this cult to the unsuspecting medical students from Vietnam. It is a remarkable phenomenon that the therapy of acupuncture is practiced by physicians with M.D. degrees in competition with the equally mystic and ancient Chinese witch-doctor practice of vacuum-cup therapy. An even more serious deterrent to the practice of modern diagnostic medicine is the failure of the French to develop clinical pathology under medical direction, as have their neighbors, especially in England.

As in France the pharmacist in Vietnam receives inadequate training in medical technology and is assigned the responsibility of running the hospital laboratories, resulting in a philosophy of medical care almost completely independent of the laboratory and oriented toward the response of patients to therapy.

Since both surgical and necropsy pathology are well developed in France it is difficult to explain the almost complete disinterest in autopsy examinations in Vietnam, especially since there are no important religious objections. There is an obvious need of developing the self analysis, postgraduate teaching, and group-discipline way of medical life associated with necropsies in hospitals throughout this country.

A diligent attempt is being made to correct this situation through United States Agency for International Development—AMA Medical Education Project, which has been under the very capable direction of a widely known Minnesota surgeon, Norman W. Hoover, formerly on the orthopedic staff at the Mayo Clinic.

Arthur H. Wells, M.D.
Duluth, Minnesota

*See page 909.



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Prisoners of War

Living in the most opulent society the world has ever known, it is not easy for us to put ourselves in the place of, and think like, a prisoner of war.

One physician who did try to understand the prisoner of war was the late Dr. Leslie Caplan, himself a prisoner of the Nazi Germans in World War II and whose subsequent career was permanently colored by this experience. It is not unlikely that his decision to enter psychiatry was influenced by his tortured life at the hands of the Nazi Germans. He developed the thesis that all veterans who have been prisoners of war should receive service-connected disability.

In September 1969 a symposium was held at the Minneapolis Veterans Administration Hospital to honor Dr. Caplan. Two of the papers presented at this symposium are published in this issue.

Leslie Caplan was a flight surgeon on a mission out of Italy flying over Vienna in a B-24 in October 1944 when his plane was hit. The crew bailed out over Yugoslavia where he was taken prisoner. He was sent to Pomerania where, in February 1945, his entire camp of 2,600 men were marched out on a journey covering 600 miles in 86 days. Freezing, living in filth, disease and on a starvation diet, it was a nightmarish experience ending only in liberation by the allied armies on May 2, 1945.

Lumry* cites the evidence that prisoner experience in general and in concentration camp life in particular leads to permanent damage to the individual. Halloran† emphasizes the surprising difference between the American prisoner of war of World War II and his counterpart in the Korean war. The World War II prisoner maintained morale in the face of overwhelming difficulties, exemplified by the experience of Leslie Caplan. The American prisoners in Korea, on the other hand, showed morale deterioration and lack of inspiration to escape, and died in shocking numbers. A group of Turks similarly incarcerated had no deaths. There is no doubt that the differences of American behavior in these two conflicts and the behavior of other groups such as the Turks will be the subject of study for years to come.

Reuben Berman, M.D.
Minneapolis, Minnesota

*See page 915.
†See page 919.

Value of Routine Chest X-Ray on Hospital Admission

In this enlightened age of medical science when the public expects a high degree of sophistication from its physicians, it is distressing how frequently elementary procedures are omitted. Roentgenographic examination of the chest is simple and inexpensive; yet large segments of our population do not get the benefits of this procedure. The article by L. M. Hammar* reports experience with routine roentgenography on hospital admission in a community hospital. It illustrates at least two significant points: (1) the appreciable incidence of unsuspected abnormality and disease found, and (2) the surprising reluctance of some physicians to utilize this opportunity.

As the incidence of tuberculosis has declined in this country in recent decades, mass surveys using chest roentgenograms have received less emphasis. Today, conditions other than tuberculosis are identified with greater frequency, although tuberculosis continues to be an important public health problem in some communities. In addition to its use as a diagnostic procedure, roentgenography is important in establishing a base line from which future change can be measured. Comparison of heart size, recognition of duration of pulmonary granulomas, or awareness of other variations becomes an essential public health practice in continuing care of patients.

David R. Sanderson, M.D.
Rochester, Minnesota

*Hammar, L. M.: The Admission Chest Film Program: Fifteen Years' Experience. Minnesota Med 52:1899, 1969.

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When Faltermayer* states that "the majority of physicians operate as entrepreneurs and constitute an army of pushcart vendors in an age of supermarkets," he is grossly unfair and, from a physician's standpoint, it would appear that he has had his eyes focused on the distant past when medicine had no more than a handful of specifics.

He criticizes the fee-for-service method which involves separate billing for visits to doctors for shots, x-rays, laboratory tests, surgery, anesthesia and hospital room. This of course is merely a denigrating cliche, for certainly the whole of America works on a "fee-for-service" basis. We pay for the items we purchase whether through contract or on the basis of a price tag. No matter how we lump it, it is a fee-for-service.

Faltermayer further mentions that "for a patient simply to find medical care can be maddeningly difficult." Certainly no more difficult than searching for an item in a "supermarket" where you ask the boss where it is and go and get it! He would make it seem that the patient would prefer to obtain the services of all and any specialists in one individual so as to eliminate the "maddening difficulty" of finding the man who is most qualified. Is he not at liberty to ask his family physician for a consultation at any time? In the horse-and-buggy days when a doctor was scarcely more than a "pushcart vendor," the critical advocate of reform no doubt wanted specialists of all degrees but, now that he has them, he does not want to take the time to ask for one.

Faltermayer also states that "the real propellent, forcing up costs, is the archaic manner in which medical care is arranged and paid for—on a piece-work basis in which doctors profit by prescribing more elaborate care than is needed." Here again he is being almost diabolically paradoxical, critical on the one hand because doctors fail to take proper care of the individual, and on the other hand critical because in modern medical practice it is necessary to have numerous piece-work items done here and there or in the doctor's laboratory, all of which costs money.

Fortune further states that "medical manpower and facilities are so maldistributed that large segments of the population, especially the urban poor and those in rural areas, get virtually no care at all."

More often the patient, who is medically unqualified to make the decision, demands more treatment than a physician recommends and, if it is not forthcoming, searches and shops around until he finds someone who will accede to his demands. An honorable doctor will not prescribe more than is needed.

Instead of being criticized doctors should be praised for having devised methods by which twelve separate determinations are made for the ridiculously low cost of $6.00 (formerly $80.00). "The biggest factor in rising health costs is the growing use of increasingly expensive hospitals." This the doctors recognize and can do nothing to control. It is merely the shop in which they work. Graphs in Fortune's criticism of the medical profession indicate that physicians' fees over a period of ten years have risen from an index of 100 to an index of 150, whereas hospitals' service charges have risen from the same figure to an index of 250. Those who read only the headlines fault the doctor; those who peruse the contents make a truer evaluation.

Dan Cordez* in the same issue of Fortune states that the number of physicians caring for private patients in 1965 was 9.2 per thousand Americans, but that specialization took its toll and dropped the number to 5.0 per thousand. He then compared this figure with that of 1930 when there were 13.5 physicians per thousand.

*Edwin K. Faltermayer, Dan Cordez, Fortune, January 1970.

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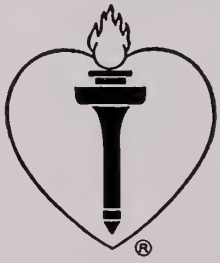
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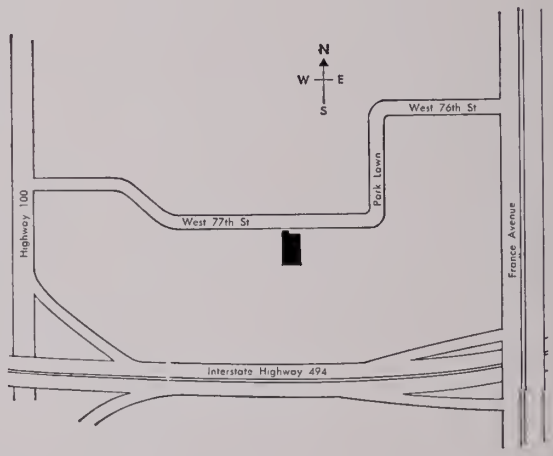
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This is flagrant distortion, for when that ratio existed the general practitioner in 1930 was attending most of the specialists' problems in addition to his own. Draining these specialists from the ratio does not constitute an indication of less adequate care, because the patient is now receiving attention for his specialized disease by a man who is particularly qualified.

Cordez further states: "For the past two or three decades all the country and its medical needs changed radically, most medical schools have remained virtually the same." What an irrational statement this is, for any physician who graduated in 1930 well knows that unless he had kept up on his medicine with diligent and ceaseless study and reading, his 1930 top knowledge would scarcely be sufficient to admit him into a medical curriculum of 1970. With the recent numerous developments: new drugs, antibiotics, operations and advances in all fields of medicine and the accrued benefits therefrom, the medical needs for better health have diminished and any statement to the contrary is grossly unrealistic.

The training of a whole generation of new doctors year after year has not become increasingly inadequate but has progressed with the times and with the advance of science in all fields. The teaching methods in the field of medicine cannot be compared to the teaching methods of the public schools. Learning that which is new in medical science cannot be accomplished by the machinations of changing curricula and expensive bureaucratic regional planning but only by the diligent, daily, concentrated study that has become habitual with every worthy physician.

"Because of the wide gap between their education and that of others in the medical field doctors routinely perform many tasks that are beneath their level of competence." This is very improbable; it is much more likely that doctors teach and assign to their nurses, laboratory technicians and other para-medical workers the privilege of preliminary history taking, social economics, vital statistics, blood pressure, pulse, temperature, shots, dressings, laboratory tests, and the numerous other procedures that "are beneath the level of the doctors competence."

The continuously unfair criticism that the doctor receives creates a bad image; but, despite this, the physician on the whole continues to give his patient excellent professional care. The highest cost of medical care should be laid at the door of redundant para-medical personnel: the multiplicity of bureaucratic demands, administrators, hospitals, and the people that man them. Perhaps the situation cannot be altered, but it would go a long way to settle the emotions of a host of dissatisfied people if the credit and blame were assigned to the proper areas.

Carl O. Rice, M.D., Ph.D.
Editor-in-Chief

Intra-Aortic Balloon Pumping: Limitations and Advantages*

Over the past decade considerable interest has developed in, and extensive research efforts have been devoted to, methods of providing temporary assistance to the failing myocardium. Of the many techniques for mechanical support of the circulation that have been proposed, one of the more ingenious and at the same time simplest procedures is that of intra-aortic balloon pumping, a technique conceived by Moulopoulos and associates in 1962.[1] These investigators report their latest studies in the March issne of Minnesota Medicine.

A catheter-balloon system is introduced into the intrathoracic aorta via a peripheral artery (femoral or carotid). The balloon is rapidly inflated with carbon dioxide during ventricular diastole, thereby increasing aortic root pressure and improving coronary blood flow. Deflation of the balloon occurs during ventricular

*Moulopoulos, S. D., Kwan-Gett, C. S., Collan, R., and Kolff, W. J.: Intra-Aortic Balloon Pumping: Its Effect in Sheep with a Ligated Coronary Artery. Minnesota Med 53:261, 1970.

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systole. The extracorporeal apparatus is relatively simple and consists in part of a control device that times inflation and deflation of the balloon according to the R wave of the electrocardiogram. It is essential that the balloon fill and empty quickly through the long catheter system and that balloon inflation be accurately phased with the electrocardiogram. Various modifications in their apparatus are described which have decreased the incidence of problems associated with previous models.

The authors have answered one of the criticisms leveled at previous experimental trials, namely, that only healthy animals have been used, by producing acute left heart failure in sheep by ligating the anterior descending coronary artery. In their experimental preparation they clearly show a beneficial effect on the circulation (increased aortic blood flow and pressure) for both balloon pumping and left atrial-aortic bypass, particularly the latter. Although balloon pumping improved flow and pressure, it did not always lower the left atrial pressure nor did it always prevent the occurrence of ventricular fibrillation.

Heparinization is not mentioned, but heparin must have been given at least to those animals which underwent left atrial-aortic bypass, and heparin has been used by other investigators in the balloon technique to prevent the formation of nonadherent clots that can be disseminated as emboli. The continued use of large doses of anticoagulant may become a problem during clinical application of the technique.

A potential hazard is rupture of the balloon and introduction of carbon dioxide into the vascular system. Difficulties may also arise in diseased aortas and peripheral vessels, preventing catheter passage to the desired location. A beating heart is a requisite for application of this technique.

One of the main limitations of balloon pumping for human use, as emphasized by the authors, is its inability to be used effectively at rapid heart rates or in the presence of atrial fibrillation with a fast ventricular response. Clinically, most patients in shock do have tachycardias with varying degrees of irregularity, making it necessary in some cases to manipulate the cardiac rhythm by the use of coupled pacing or paired pacing, techniques that are not entirely without hazard themselves. In addition, all forms of assisted circulation are critically limited by the duration of assistance that can be applied. The tolerance to total or partial cardiopulmonary bypass is inversely related to the perfusion time, yet most serious abnormalities of myocardial contraction are not likely to be reversed in a few hours. In this report the beneficial effects of balloon pumping ceased soon after pumping was stopped.

In spite of these limitations this work is of considerable interest, as it does demonstrate that under selected experimental conditions assisted circulation can be used to maintain life, for short periods of time at least, when all other measures fail. The method is simple and appealing for acutely ill patients in whom extensive manipulation is to be avoided but in whom mechanical assistance for the circulation is necessary.

There is a real need in the clinical area for effective methods of safe assisted circulation that may be continued long enough to permit recovery of the myocardium for such potentially reversible insults as acute myocardial infarction; but, in spite of extensive interest in assisted circulation for many years, clinical experience to date has been meager and often disappointing. It is hoped that continued improvements in assist devices such as those reported by these authors will improve the outlook for the future. The results of clinical trials are anxiously awaited.

Gordon K. Danielson, M.D.
Rochester, Minnesota

Reference

1. Moulopoulos, S. D., Topaz, S. R., and Kolff, W. J.: Extracorporeal Assistance to the Circulation and Intraaortic Balloon Pumping. Trans Amer Soc Artif Intern Organs 8:85, 1962.

Genius is one percent inspiration and ninety-nine percent perspiration.—Thomas A. Edison.

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Estimation of Lung Size, Muscle Strength, and Lung Growth in Scoliosis*

A NUMBER OF interesting points and questions are raised by this article. Comments will be limited, however, to three areas.

1. The author comments on the difficulty of predicting lung volume from body height in subjects with thoracic deformity. He chooses to use height rather than arm span. In this study where change in volume is of major interest the predicted normal value is of less interest. However, in the overall evaluation of a patient with kyphoscoliosis, for example, accurate prediction of normal value is important. Use of height results in falsely-low predicted value, whereas use of arm span provides a much more accurate estimate of the impairment of lung volume.

2. The author has made estimates as to the normality of cough. Although the flow resistance of the airways is important to the cough mechanism, so also may be the strength of the respiratory muscles in patients with scoliosis or other neuromuscular disorders. Recently Black and Hyatt† have described a relatively simple approach to the quantification of respiratory muscle strength which could be applied profitably to patients with scoliosis.

3. Is the age at which the thoracic deformity occurs important in determining the degree of pulmonary parenchymal impairment? Several studies‡ indicate that the lung continues to add new alveoli, possibly into the early teens. However, there are no longitudinal studies on normal children to document the usual pattern of lung growth and the variability among individuals. It is possible that the time of development of the deformity may be significant in terms of the final degree of pulmonary impairment. This is just one example of the need for a careful longitudinal study of the growth of pulmonary function.

Robert E. Hyatt, M.D.
Rochester, Minnesota

*Westgate, H. D.: Pulmonary Function in Thoracic Scoliosis Before and After Corrective Surgery. See page 839.
†Amer Rev Resp Dis 99:696, 1969.
‡Dunnill, Thorax 17:329, 1962; Emery and Walcock Acta Anat (Basel) 65:10, 1966.

Test Your Word Score

Glycolysis—*decomposition of sugars in the metabolism (Page 925).*

Hypertelorism—*abnormal distance between two paired organs (Page 891).*

If an executive hasn't enough sense to take care of his own health, he hasn't enough sense to supervise other people, commented the head of a large Midwestern company. Recent survey of five hundred apparently healthy business leaders showed 41% suffered from ailments of which they were unaware; 71% had some physical abnormality; 52% were in need of immediate treatment; 11% "knew something was wrong" but "didn't have time to seek medical advice."*

*Newsweek.

Man is the only animal that can be a fool. —Holbrook Jackson

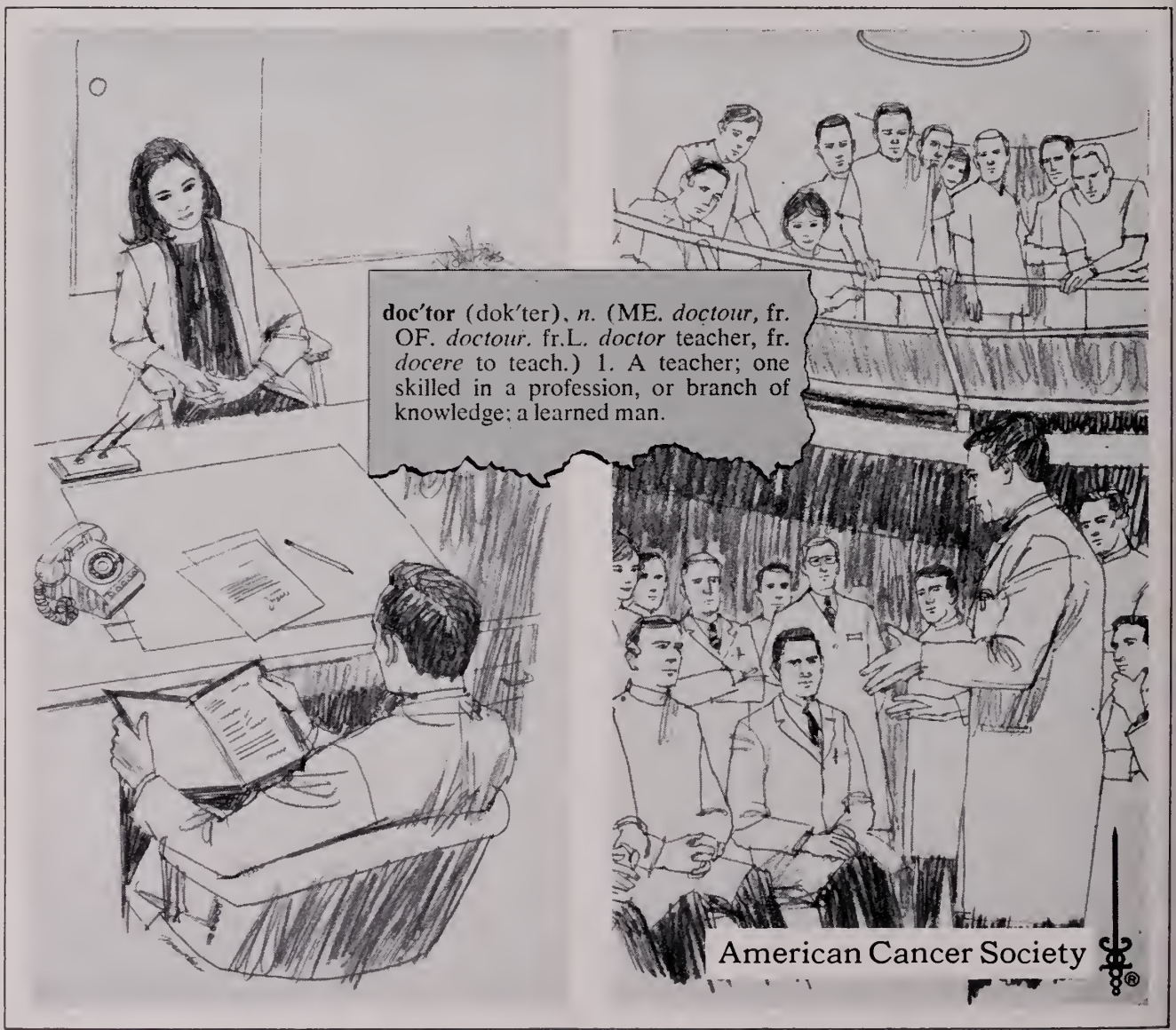
The Doctor

One of the doctor's most important roles is in education.

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Assisting the doctor in his teaching role is a major function of our professional education program. Through medical conferences, films, exhibits, pamphlets, monographs and other publications, we provide him with the most important and current information on cancer.

If, as Henry Brooks Adams speculated, "A teacher affects eternity; he can never tell where his influence stops", the outlook is optimistic.



You May Be Right

Antibiotic Sensitivity Patterns

Dexter and Bates* try to provide meaningful data for clinicians by computer tabulation of the antibiotic sensitivity patterns of the organisms isolated at their hospital. This is a task that should be performed by all hospital laboratories so that the members of the medical staff of that hospital can select the appropriate antibiotic for the organism encountered. Unfortunately, the method of antibiotic testing used in the article was strictly a qualitative method subject to very misleading results. Thus, computerized data can also be misleading.

Disc sensitivity testing has been standardized well and is highly reliable when done by the method described by Bauer, Kirby, Sherris and Turck in 1966. This method has been pictorially described for the laboratory in Hospital Practice, Vol. 5:91-100, Feb., 1970. The American Society of Clinical Pathologists has organized regional workshops to help laboratories learn this method or other reliable methods of antibiotic testing. One of these was held at Methodist Hospital in St. Louis Park on January 17, 1970. A film describing this method of disc sensitivity testing is also available from one of the pharmaceutical companies. It is no longer permissible to place a disc of an unmeasured potency on any media and report sensitive or resistant on the basis of any small zone of inhibition. This has repeatedly been shown to be misleading when tube or agar dilution sensitivity tests have been compared.

Sulfa sensitivity tests can be done with the standardized method, are reliable, and correlate well with the clinical situation. Obviously the 90% resistance reported in the article was incorrect, as most centers using reliable means of testing for sulfa sensitivity report ⅔ to ¾ of the strains of E. coli to be sensitive to sulfa drugs.

By controlling the variables of disc sensitivity testing, the procedure can be a highly reliable technique correlating well with tube or agar dilution methods. Without such controls, the results can vary from misleading to meaningless.

It is the responsibility of the hospital pathologist to upgrade the bacteriology portion of the laboratory in keeping with the tremendous strides made by most laboratories in chemical techniques over the past few years.

With reliable methodology and computerized data, all clinicians will be able to have information at their fingertips regarding their own hospital situation and thus be totally independent of pressures from pharmaceutical companies to use antibiotics which may or may not be appropriate for the situation.

Dr. John Matsen had a very complete article in this journal (Minnesota Medicine Vol. 52: 1499-1503, Sept., 1969) describing antibiotic disc testing. Thus, this recent publication by Dexter and Bates should perhaps have been published in a history of medicine section or a section entitled "Retreat." It certainly is not an advance.

Don P. Amren, M.D.
Minneapolis, Minnesota

*J. F. Dexter and H. A. Bates: Antibiotic Sensitivity Patterns of Staphylococcus and Gram-Negative Bacteria. Minnesota Med 53:205, 1970.

Birds

Protect the birds. The dove brings peace and the stork brings tax exemptions.—Birmingham News



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The Editor's Soliloquy

The Social Hour

It is at the combined social hour after the committee meetings and before the dinner when many of the problems that are bothering you are solved. It is here that you meet your friends and find an opportunity to greet one another, reestablish amenities, crystallize a few ideas from the last conversation, smooth over the rough spots from a previous conflict, or disperse an imaginary slight.

As you enter the meeting room for the social hour you find a few of the well seasoned, semi-retired affable gentlemen cozying themselves comfortably in an offside chaise longue where they reminisce or philosophize among themselves and receive the salutations of their younger upcoming peers.

Off to one side you will perceive the secret three huddled with hands vehemently gestulating and elbows protruding to protect their flanks from the intrusion of the curious. They are, often, the ones who have made the decisions, shortly to be acted upon in accordance with the democratic principles of parliamentary regulations and within the rule of the newly and nigh annually revised Constitution and By-Laws.

Hovering around the hors d'oeuvres you find the corpulent and the teetotalers, as if dinner had been called off or postponed, perhaps never to be served. "Umm, 'stho goodfi uh-hu, will you have one?"

The in-town speaker of the evening is left to his own devices; he has friends, critics, advocates—sink or swim—he's been around with that talk of his before, in the staff room, the dressing room: "Do your stuff, my man, nice to see you!"

But the out-of-town speaker (in-town in his own bailiwick) is being squired through the crowded fifteen-foot radius adjacent to the refreshments, to be introduced to the hoi polloi: the chiefs-of-staff, the senior surgeons, the professor from the University, the Executive Secretary, and the very humble man "who does all the work around here."

With left arm held high the program chairman signals another honored guest, forewarning the speaker of the evening: "I especially want you to meet Mr. Greenbuck whose benevolence and spirit of fair play has endowed our project."

Later the meeting is called to order and "with your forbearance we shall read the (boring and detailed) minutes of the last meeting and the decisions of your very hard-working committees—Dr. Upinthechairs, will you proceed?" —"Do I hear a second? Any discussion? All in favor ..... signify by saying 'Ay,' all opposed 'No.' Carried! I'm sorry, George, you're overruled."

Carl O. Rice, M.D.

OLD DOC HESS SAYS: Fear not the threat of becoming legally liable, for if in the practice of your profession you are intellectually honest, you will in all probability be legally correct.—C.O.R.

Rain

If I were running the world I would have it rain only between 2 and 5 a.m. Anyone who was out then ought to get wet.—William Lyon Phelps

Five Score and More

(Continued from Page 854)

out spectacles." Never capitulating, but finally depleted, the grand patriarch and great humanitarian succumbed to bronchial asthma, but not without asking at the last moment whether he had left anything undone, such as, for instance, the signing of an important check.

"My dear fellow, I don't need it. I could go to the masthead yet." So spoke The Father of the British Fleet, **Admiral Provo Wallis** (1791-1892), in declining assistance in mounting a stile when an octogenarian. Signed up for the navy at the age of only four, he later became the youthful midshipman aboard the Shannon who, with heroism and finesse and to his everlasting glory, escorted the defeated American Chesapeake from Boston Harbor to Halifax in 1813 after both his superior officers had been disabled in the engagement between the two ships. After 54 years at sea in the old wooden vessels he continued to feel nostalgic about them even long after they had become obsolete. Hard work, careful living, regular habits, fresh air, simple food: these constituted his daily regimen. When asked how he had stood the strain of his gala one-hundredth birthday party, he replied tersely: "Getting on for one hundred and one, my boy." But death, due to mortification of the left foot, prevented him from reaching that one-hundred-and-first birthday.

Next in our group of venerables we meet **Henry Pitman, Physician,** organizer, administrator, modernizer in medical fields, illustrious for his long and distinguished tenure at London's St. George's where almost single-handed he conducted a gallant fight against a cholera epidemic that invaded the Hospital. Pitman maintained his physical and mental integrity right up to the door of death. He never wore out; he didn't fade away; an accident snapped his last link with life in 1908, 100 years after his birth in 1808.

Finally we encounter **General George Higginson** (1826-1927), valiant soldier of the Crimean War and author, when nearing his ninetieth year, of "Seventy-One Years in a Guardsman's Life." His intrepid military service lasted for fifty years and his retirement was one long series of official appearances on countless ceremonial occasions, for which he maintained physical fitness by the daily use of Indian clubs. As a nonagenarian he was thus described by the London Times: "Sir George Higginson would have some difficulty in persuading anybody of the length of his years. He may possess a wrinkle or two to support the evidence of the baptismal register, but, if so, one forgets them in looking on the lean, healthy face, which, with its heavy eyebrows and moustache, conveys only the pleasantest hint of age. It could be urged also against the mere numerical fact, that he walks his mile, takes the chair at meetings, speaks in public, and in private—remembers."

Now reducing what we have learned about each of these notable men to the lowest common denominator for all: Without exception they maintained physical and mental activity right up to the close of their lives. All practiced moderation, exercised self-discipline, avoided excess or abuse. Above all else, however, what strikes the keen observer most forcibly is that none were introverts. No morbid regret, despondency, egocentrism, self-pity, neuroticism, or senility marred or profaned their terminal years. Advanced age with dignity rather than old age with decay was their significant and unique achievement.*

*With acknowledgments to W. Forbes Gray: Five Score, 1931.

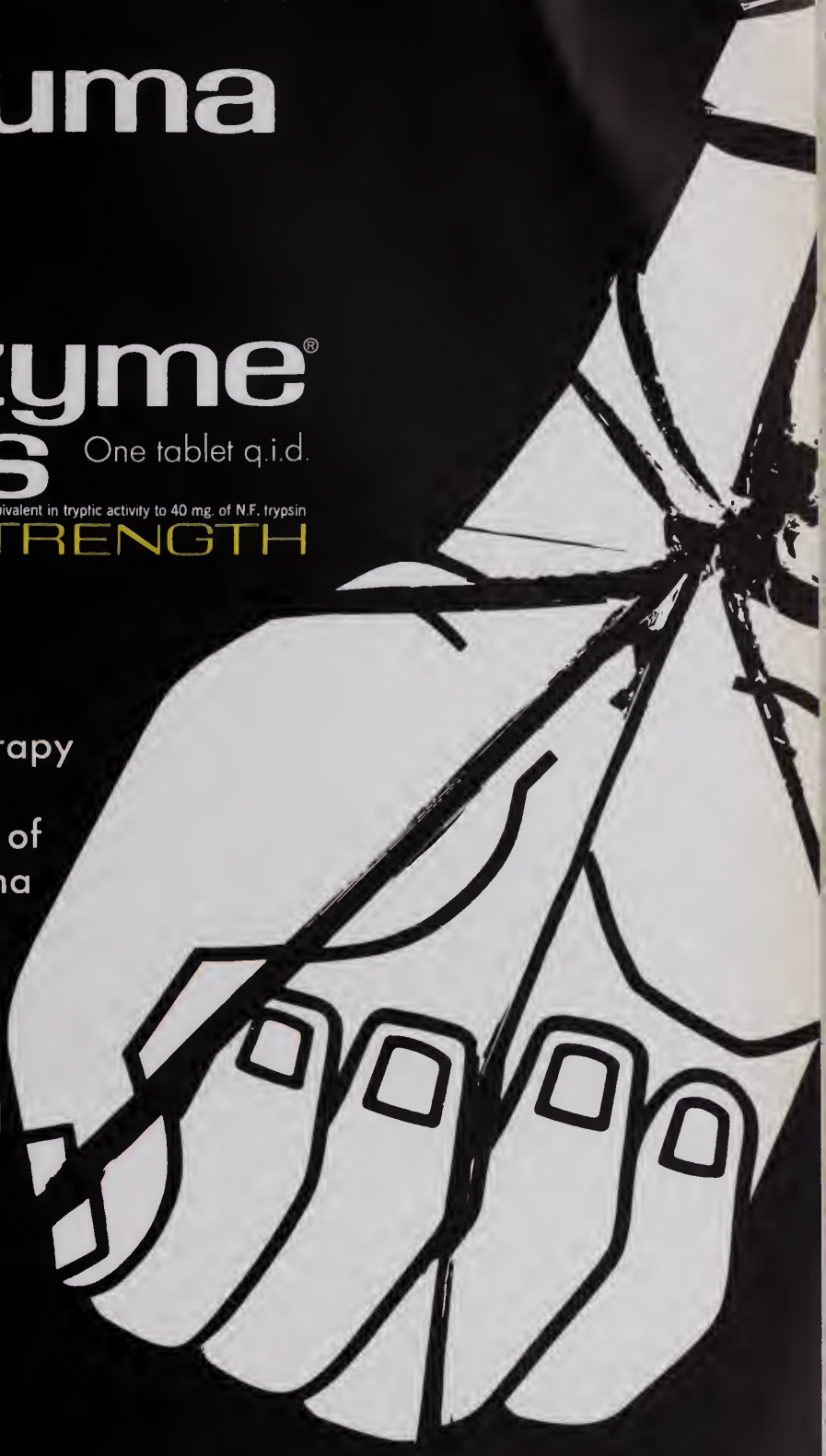
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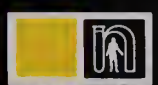
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References: 1. Gardner, H. L.: J. Miss. M.A. 8:529, 1967. 2. Porter, P. S., and Lyle, J. S.: Arch. Dermat. 93:402, 1966. 3. Walsh, H.; Hildebrandt, R. J., and Prystowsky, H.: Am. J. Obst. & Gynec. 93:904, 1965. 4. Vaginitis and the Pill: J.A.M.A. 196:731, 1966. 5. Guerriera, W. F.: South. M.J. 56:390, 1963. 6. Seelig, M. S.: Am. J. Med. 40:887, 1966. 7. Today's Drugs, New York, Grune & Stratton, Inc., 1965, p. 316. 8. Gray, L. A., and Barnes, M. L.: Am. J. Obst. & Gynec. 92:125, 1965. 9. Solerno, L. J.; Ortiz, G., and Turkel, V.: Vaginitis: A Diagnostic and Therapeutic Approach, Scientific Exhibit, presented at the 115th Annual A.M.A. Convention, Chicago, Illinois, June 1966. 10. Walsh, J. C.; Sheffery, J. B., and Wilson, T. A.: Med. Ann. D.C. 37:358, 1968. 11. Nugent, F. B., and Myers, J. E.: Pennsylvania Med. 69:44, 1966.

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Biomaterials

Thrombus Formation on Polymeric Materials

II. Blood Compatible Surfaces

DOUGLAS A. OLSEN, Ph.D.* and HAROLD D. KLETSCHKA, M.D.†

THE SURFACE PRESENTED by an artificial organ is different from that of the normal endothelium, and various changes occur in the cellular elements and proteins of the blood as a result of contact with this new surface. If these adverse reactions are to be controlled and new surfaces prepared, the blood-material interactions must be understood at the molecular level. The following discussion briefly reviews recent investigations of surface phenomena pertaining to the blood-polymer interface.

The list of polymers (plastic as well as elastomeric) tried or used in medical or surgical applications is extremely long. In fact, it includes virtually all major classes of polymers: the cellulosics, cellulose derivatives, polyesters, polyolefins, polyamides, vinyls, epoxies, phenolics, acrylics, fluorinated polymers, and the silicones. Both thermoplastic and thermosetting materials are represented. The various forms used include molded articles (both reinforced and nonreinforced), films, fibers and woven structure, and, in certain instances, fluid materials that can be polymerized or formed in place.[1] The general tendency of all polymers is to initiate clots. In time, clot formation can cause malfunction in an implanted device, such as a heart valve, by slowing or blocking its action. An equally serious disadvantage is the fact that some or all of the clots may slough from the prosthesis and be carried through the vascular system to some distant point where a clot may block an artery with consequent serious results.

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†Department of Surgery, Veterans Administration Hospital, Montgomery, Alabama.

Reprints may be at the end of this series from Dr. Olsen at: 4106 Linden Hills Blvd., Minneapolis, Minnesota 55410.

See Part I, July issue, page 773.

Wettability

Of the surface characteristics thought to be of importance, wettability received the earliest attention. Lampert[2] determined that the coagulation time of blood on a variety of surfaces (glass, metal, paraffin, phenolformaldehyde polymer, etc.) is inversely proportional to the wettability of the surface, i.e., the attractive forces existing between the blood and the surface. With a glass surface, which is quite wettable, coagulation time is faster than with a surface coated with the relatively nonwettable paraffin. Subsequent workers also obtained data which, in general, they interpreted as following "Lampert's rule."[3] Rose and Broida[4] determined whole blood clotting times on a variety of surfaces and concluded that Lampert's simple concept did not hold. It was also noted that repeated determinations on siliconized glass with only a saline rinse between measurements showed a rapid decline in clotting time. It would appear, therefore, that a change in the surface was occurring as a result of a slow adsorption of some species. Ross et al.[5] also showed the inadequacy of the concept of Lampert relating clotting to the wettability of the surface. Since there are several substances which can be adsorbed on the surface, there can be no such correlation of wettability with clotting time unless an absolute wettability factor can be ascribed to any surface. Work to be reported in a subsequent section shows that Zisman's concept of the critical tension of a surface[6] provides an absolute wettability and appears to correlate with clotting times of blood.

Surface Charge Characteristics

The charge characteristics of a surface in contact with blood are undoubtedly important if for no other reason than that of the naturally-occurring negative charge on the vascular interface.[7,8] It is generally accepted that the vascular lining (intima) is an anionic mucopolysaccharide.[3] The presence of a negative electrical potential due to the anionic groups has been found to inhibit initiation of clotting.[8-12] Intima has a net charge of −3 to −13 millivolts.[13,14]

Electromotive Series

Sawyer[15] carried out several experiments *in vivo* to test the hypothesis that intravascular thrombosis is related to a critical interfacial potential. The hypothesis predicted that tubes constructed of magnesium, aluminum, and other metals placed toward the more active end of the electromotive series would be antithrombogenic, while stainless steel and copper tubes near the more noble end would display an increased rate of thrombosis. Silver tubes and platinum tubes were also evaluated. These tubes were inserted into either the canine descending aorta or the thoracic inferior vena cava. Sawyer noted that magnesium, aluminum, and molybdenum tubes from the upper end of the electromotive series displayed little tendency to thrombose. Regarding the tubes fashioned from materials at the more noble end of the electromotive scale, mean patency time for the stainless steel tubes approached 20 days, that for copper tubes less than seven days, and for silver and platinum tubes, two to three hours and less than one to two days, respectively. All of the metals tested exhibited very destructive effects on the blood elements as shown in the Table.

Electrostatic Charge

Sharp[16] has stressed that there is significance in the electrical potential of a synthetic material with respect to blood clotting tendencies. If the material is negative, Sharp suggests that it reacts to a lesser degree to the blood elements and, therefore, diminishes its thrombogenic action. A "bio-electric" polyurethane having a naturally-occurring negative static potential was considered to be the most promising polymer. Schwartz[17] suggested that venous thrombosis is enhanced under experimental conditions by decreasing the relative negativity and is inhibited by an increase. The significance of these findings is open to dispute, since Ross et al.[5] found that surface charge measured *in vitro* correlated poorly with *in-vivo* clotting.

In a somewhat related study, Gott et al.[18] examined various materials in an attempt to obtain a selective adsorbing surface and to dispel any electrostatic charge on the polymer surface. Their *in-vivo* data obtained by inserting uncoated rings made of various polymers into the blood vessels gave the following order of decreasing clotting time.[3,18]

> Silicon-coated polymethylmethacrylate > Polychlorotrifluoroethylene > polyethylene (high density) > polytetrafluoroethylene > polymethylmethacrylate > polyethylene (low density), polypropylene, polyvinyl chloride, polycarbonate of bisphenol A > polyoxymethylene.

In general, the more chemically polar surfaces gave shorter clotting times.

TABLE
Changes in Blood Elements after One Hour Interface with Different Disc Surfaces*[15]

Parameter	Magnesium	Magnesium Alloy AZ31	Stainless Steel	Plastic†	Aluminum
R.B.C.	84%↓	48%↓	28%↓	27%↓	8%↓
W.B.C.	59%↓	10%↓	21%↓	14%↓	7%↓
Platelet	100%↓	77%↓	64%↓	92%↓	74%↓
Plasma Hemoglobin	↑2600X	↑1111X	↑189X	↑124X	↑64X
Albumin	82%↓	72%↓	36%↓	19%↓	31%↓
Gamma Globulin	84%↓	80%↓	53%↓	9%↓	15%↓

*In decreasing order of destructiveness.
†Polycarbonate.

Zeta Potential

In further attempts to delineate the possible effects of surface charge with blood clotting effects, Ross et al.[5] also tried to correlate the zeta potential of various plastics in contact with Ringer's solution with the thrombogenic qualities of the polymers, but they were unable to demonstrate a cause and effect relationship. Furthermore, attempts by others[16,19] to relate a negative zeta potential to nonthrombogenic qualities of polymers met with failure for reasons similar to those experienced by Ross et al.[5] who had previously found that the adsorption of materials on the surface of a polymer cancelled out the inherent wettability characteristics of the polymer itself. Mirkovitch et al.[20] and Leininger et al.,[19,21,22] in their studies in connection with zeta potentials, found that an initially negative charge on the polymer quickly shifted upon contact with blood, plasma, or blood proteins. This shift in charge was due to the adsorption of blood proteins on the polymeric surface so that the solution was no longer in contact with the surface of the polymer, but rather with an adsorbed layer of protein on the surface. Generally, detailed studies of zeta potentials of various polymers have shown little correlation with clotting tendencies.[23] Furthermore, it has been observed that the zeta potential of all plastics measured *in vivo* tends toward zero when in contact with blood.[22]

Electrets

The antithrombogenic properties of electrets have been considered.[24,26] An electret is formed by solidifying molten polymer in either a high intensity electric field or a magnetic field, thereby inducing a permanent charge on the polymer surface. In general, surfaces with negative charge resist thrombosis while those with positive charge promote thrombosis.[25,27] While the concept is novel, the results so far are inconclusive.

Geometry and Surface Smoothness

The smoothness of a surface has been held important in the prevention of clotting, but even very smooth surfaces, such as glass, are thrombogenic. Less smooth surfaces have increased thrombogenicity, probably through the creation of turbulence, which culminates in mechanical damage to the blood. In addition, the thrombogenic potential of a given smooth or rough surface depends on the site of its implantation and the conditions under which it is exposed to the blood. For example, Kolff[28-30] found that aortic grafts with smooth surfaces exposed to the blood clotted, whereas those with rough surfaces remained patent. The opposite situation was found to exist when the implants were placed intracardially, either as patch grafts or as mitral valves. In such cases, the rough surfaces developed clots on them, while the smooth surfaces remained free of thrombi. The possibility exists, however, that clotting may have occurred in the latter instance and—because of the smooth surface having no "hold-in power" for the clot—the clots may have broken off and embolized, leaving the surface free of thrombus. Smooth surfaces, on the other hand, have functioned well when polymers such as polydimethylsiloxane and polytetrafluoroethylene have been so fabricated and used as cannulae for kidney patients undergoing chronic renal dialysis.[29]

Hemodynamics

Smoothness in itself does not ensure that clotting will not take place on the surface of a given polymer. Other factors can alter the thrombogenic qualities of a given smooth polymeric surface; among these are blood flow rate, the diameter of the tube, blood turbulence in the vicinity of the plastic surface, and other such factors. The hemodynamics of a flowing blood system are of importance because either excessive turbulence or excessive stasis can lead to coagulation.[22] Fry et al.[21] showed that even thrombogenic surfaces may not initiate clotting if there is a sufficient flow of blood past the surface and if there is no turbulence. Smooth, streamlined thrombogenic surfaces may not clot, they point out, and rougher surfaces may increase clotting through the turbulence created. Why this occurs remains unanswered.

Geometry of Interface

The geometric form of the interface also plays a role in the thrombogenic qualities of a given surface exposed to blood. Fry et al.[31] showed that a smoothly bent glass tube re-

mained patent between an arteriovenous shunt for long periods of time, even in the unheparinized animal, whereas clotting within the tube readily took place when it was bent at a sharp angle. Somewhat related work is that of Bernstein et al.[32] and of Blackshear et al.[33] which indicates that hemolysis of red blood cells is due primarily to destructive interaction of the cells with the wall of the vessel or pump. Hemolysis appears to be proportional to the square of the rate of red cell-wall collision. Turbulence, occlusion, etc., would tend to affect this collision rate. It should be noted that Nosé[34] has discussed some of these effects as they pertain to the design of an artificial heart. The effects on the formed elements will be discussed in more detail in a later section.

Nonthrombogenic Surfaces

At this point, two research paths present themselves. The approach most useful thus far has been to bond anticoagulants such as heparin to the surfaces of materials used in the artificial organ. This approach is discussed in the remainder of this section. The other research path seeks to understand the interactions between polymers and blood and to use the results to modify or prevent the interactions. A discussion of this latter approach is best deferred until after the mechanism of blood coagulation has been discussed.

Graphite-Benzalkonium-Heparin Surfaces

The first significant advance toward nonthrombogenic surfaces came with the development of heparinized surfaces by Gott, Whiffen et al.[18,35-42] Heparin, which is the best available anticoagulant, has been bonded to an interface in an attempt to render various polymeric surfaces nonthrombogenic. Heparin is the most negatively charged organic substance in the body, and, although this characteristic has been proposed to account for its properties, its action *in vivo* is not completely understood.

In this procedure, graphite is first coated on the polymer (or metal) surface. The graphite in turn serves to adsorb a cation, usually the benzalkonium group, which then ionically binds the heparin. It is interesting to note that the charge across these surfaces is −10 to −16mV and is very close to the values reported above for intima.[43] Plastics treated in this manner are nonthrombogenic both in laboratory and animal tests. A high percentage of rings with the graphite-benzalkonium-heparin (GBH) treatment placed in the vena cava of dogs have remained clot-free for more than one year.[41]

Fourt et al.[44-46] carried out studies to determine how this effect was mediated. They presented evidence that heparin introduced on the walls could go into solution to prevent clotting. But they also showed evidence that heparin on the walls could be even more effective in preventing coagulation of blood than heparin in solution. They were unable to delineate the mechanism by which this happened, but postulated that it might result from interference with adsorption and activation of Factor XII or XI of the blood clotting sequence. However, in another study they pointed out that the testing of this possibility showed no effect in prevention of activation of the factor[47] They also noted that heparin in solution is more effective when the rate of activation is slow than when it is faster. Since the rate of activation by the graphite coating without heparin is low in itself, it was pointed out that the diffusing heparin could act like a much higher concentration of dissolved heparin. In a related study, Fourt et al.[48] suggested that the actual amount of adsorbed heparin in the graphite-benzalkonium-heparin treatment is less than $3\mu g/cm^2$. Gott and Whiffen[41] found that about 20% of the original heparin remained on a polymer at the end of three months. They also suggested that the graphite-benzalkonium-heparin surface is able to adsorb heparin from the bloodstream and thus a steady state may be reached. Intermittent doses of heparin injected into the bloodstream might be used to reinforce the graphite-benzalkonium-heparin surface. For *in-vitro* testing, however, no such steady state is reached. Instead, there is only a full logarithmic relation between the amount of heparin available on the surface and coagulation times, i.e., the more heparin available, the longer the coagulation time.[41] This points out the pitfalls of extending *in-vitro* results to *in-vivo* conclusions.

While Indeglia et al.[49] have reported using graphite-benzalkonium-heparin surfaces on tygon tubing, it is generally recognized that gra-

phite-benzalkonium-heparin coatings cannot be applied to surfaces that are flexible or elastic.[50] One method of circumventing this problem is that reported by Fourt and Fookson.[51] Here, graphite is dispersed in aromatic solvents which swell silicone rubber; after evaporation of the solvent and reversal of the swelling, a graphite coating is left. Such surfaces will adsorb 2.6 to 3.9 μg of heparin/cm^2 and are thus normal graphite-benzalkonium-heparin surfaces.

Hufnagel et al.[52] undertook studies to find more stable materials that would retain their characteristics over long periods of time, and which would themselves be incorporated into the framework of the device. Their investigations led to the development of two materials, "Hepacone" and "Hepacone-G," the former a combination of silicone rubber and heparin, the latter a combination of colloidal graphite, heparin, and rubber. Preliminary experience with the use of Hepacone has been encouraging, and the same group felt that this material had alleviated the problem of clotting to a large extent when used in the low pressure circuit such as vena caval grafts and for an arteriovenous shunt in chronic dialysis programs.

Chemical Bonding of Heparin to Surfaces

Other research efforts have sought to add a functional group to the polymer surface through which heparin may be bonded. One such approach is that reported by Leininger et al.[21,53] and by Halpern and Shibakawa[54] where the phenyl group of polystyrene is chloromethylated, quaternized, and then bonded to heparin (Figure 1).

There are also other related procedures for preparing heparinized surfaces; for example, vinyl pyridine copolymer may quaternize directly without the chloromethylation step.[55] For surfaces without a pendent phenyl group (e.g., polypropylene) radiation grafting of styrene to the surface provides the phenyl group.[50] The quaternization reactions can then proceed as above. Reaction of the surface with biradicals might provide an alternate means of incorporating such functional groups.[56]

Heparin can be covalently bonded to polystyrene through an isocyanate linkage as shown by Halpern and Shibakawa[54] (Figure 2).

In the last reaction step, heparin is attached through its hydroxyl groups.

In these reactions, heparin is bonded ionically as a quaternary ammonium salt and covalently through a hydroxyl. This is possible as shown by the proposed structure of heparin[54] (Figure 3).

The molecule has a molecular weight of about 12,000 with four to five sulfate groups per unit.

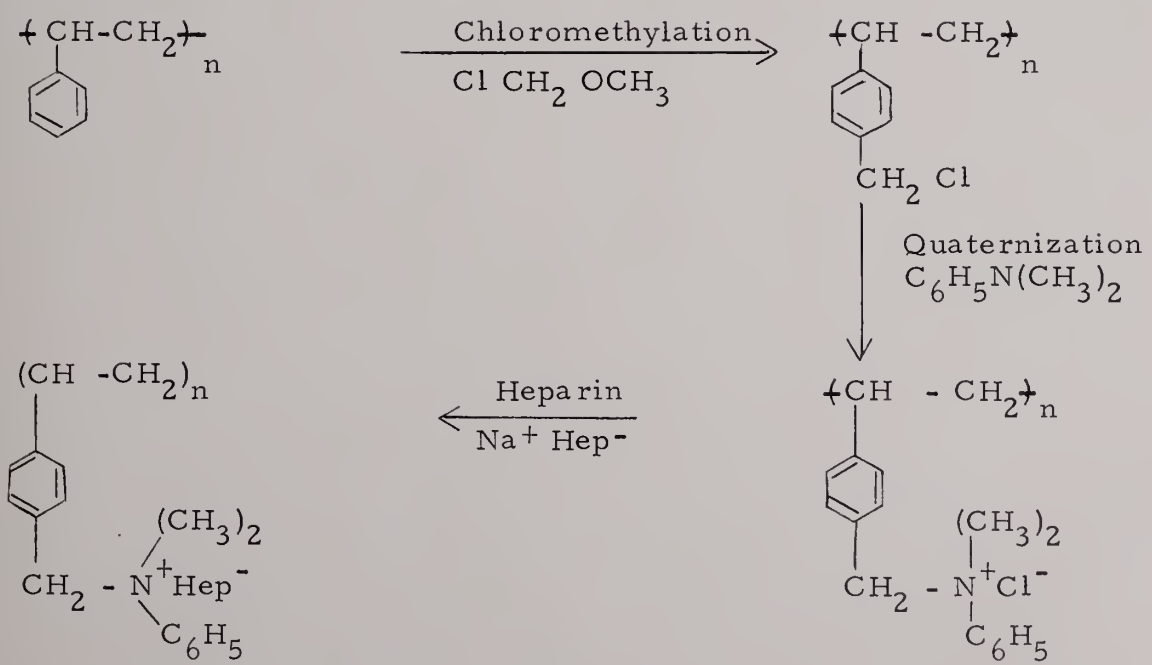


Figure 1

Other related developments have been reported by Merrill et al.[57] where ethylene imine has been reacted with cellulose surfaces to provide amine site for binding heparin. It was found that after incubating blood in cellulose-ethylene imine-heparin tubes for 70 to 90 minutes, the blood became permanently anticoagulated. Merrill and associates felt that this was due to a removal of clotting factors from the intrinsic clotting system. In addition, experiments with radioactive heparin showed that their chemically-bonded heparin surfaces were permanently coated even under conditions of high fluid shear, in contrast to the graphite-benzalkonium-heparin surfaces, which gradually lost their bonded heparin.[58] They observed that the cellulose-ethylene imine-heparin membranes achieved a powerful antithrombotic effect without loss of heparin from the surface, and without anticoagulation of the contained blood by heparin in solution.

Merker et al.[59] have reacted the surfaces of particulate silicas with aminoorganosilanes, which also provide amine groups for forming amine salts with heparin. These heparinized silicas were incorporated as fillers into silicone rubbers with only modest improvements in clotting times.

Falb et al.[50,60] have studied the permanency of heparinized surfaces using radiolabeled heparin (sulfur-35). The stability of the heparin/amine complex is affected by the structure of the amine. Their results indicated that quaternary ammonium salts are more effective in binding heparin than are primary, secondary or tertiary amines, and that amines containing alicyclic or aromatic structures are more effective in binding heparin than those containing only straight chains.[60] They also suggest that a surface layer of heparin between 100 and 200 Angstrom units thick is sufficient to prevent clotting.[50] The binding of Azure A to heparinized surfaces has also been suggested as a non-destructive colorimetric procedure.[46]

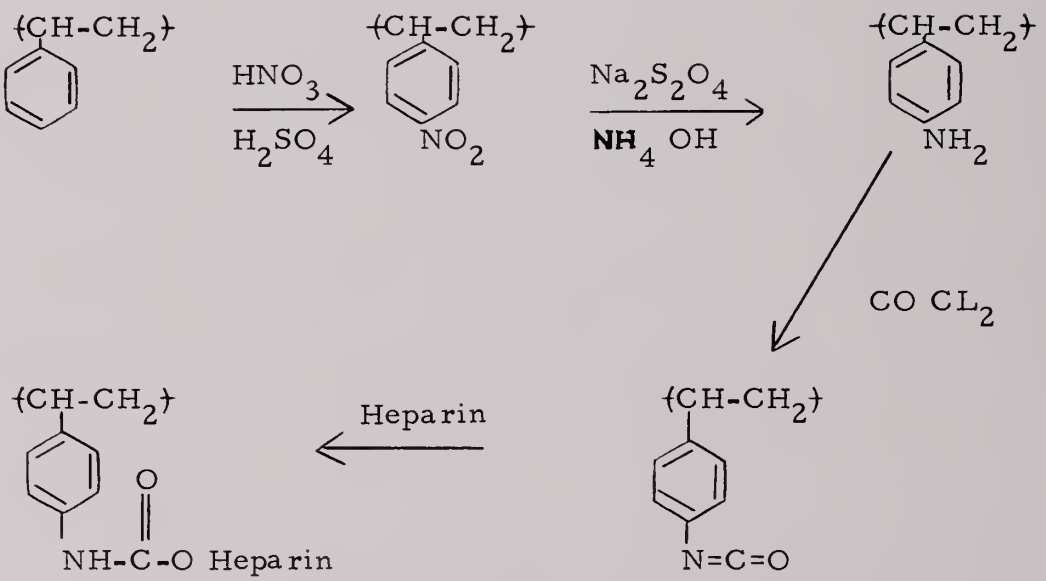


Figure 2

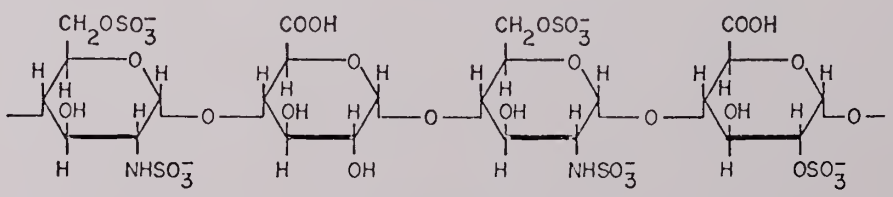


Figure 3

Rubin and Stenzel[61] note that heparin might be bound directly to collagen, without intermediate reactions, because of the many carboxyl and amino side groups on the collagen backbone. Eriksson et al.[62] have absorbed cationic surfactants onto polyethylene and polypropylene as a means of preparing these surfaces for the adsorption of heparin.

Hydrogels

Non-thrombogenic surfaces utilizing hydrogels have also been considered.[63] In this study, a number of porous acrylamide gels with a high water content (i.e., hydrogels) were prepared and tested for thrombogenicity. Only preliminary results are available; however, they indicate some promise in this approach. The rationale for the approach has been given by Hastings,[64] who has considered the surface of blood vessels to be an ideal surface. In this latter instance, the immediate surface in contact with blood is somewhat of a "slime layer," which contains heparinoid complexes. The concentration of these heparinoid complexes, however, is not high and it is not clearly understood how important they are. It is because of the existence of this "slime layer" that hydrogels were expected to show promise, the theory being that it would be difficult for proteins to be adsorbed and denaturation might be minimized. Fourt et al.[44] also studied the effects of liquid interfaces on the clotting time of blood and found that there were long delays in clotting where blood encountered liquid surfaces.

Sulfur-Containing Surfaces

Within the blood-vascular system, there appear to be recurring themes. First, there is some evidence to show that both the intima and the formed elements (including cells and proteins) are negatively charged under normal circumstances.[65] Second, Wright et al.[66] noted the recurring presence of anionic materials owing their negativity to sulfur-containing groups, such as heparin. Likewise, endothelium and endocardium contain considerable amounts of sulfated mucopolysaccharides. They cited the work of Chargaff et al.,[67] who showed that certain biological compounds such as cellulose, starch, and glycogen, can actually be invested with anticoagulant properties by introducing sulphuric acid groups into their structures. It has been conjectured that heparin acts partly by adsorption at sites of endothelial injury or on foreign surfaces (such as graphite-benzalkonium-heparin-coated surfaces) and thus restores the negative charge to those sites. Although the presumption has been that the negative charge produced would restrain platelet and protein adsorption, platelet adhesion has not been shown to be reduced by heparin. It was felt by Wright et al.[66] that the properties of endothelium which invest it with its particular ability to retard thrombus formation were more related to the chemical constitution of the natural vascular lining. They tested several substances possessing such characteristics. The two most promising were polycarbonate treated with sulfuric acid and chlorosulfonated polyethylene. Both polymers, when tested by the technique of caval implants according to the method of Whiffen and Gott[18,68,69] showed considerable resistance to thrombus formation. As an intravenous suspension, chlorosulfonated polyethylene has been shown to have heparinoid properties.[70] More recently, sulfonated polycarbonate (Lexan) was investigated and initially appeared to give anticoagulant surfaces. Additional tests showed this effect was due to lowering of the pH of the plasma, probably because of entrapped excess acid.[46]

Fibrin Surfaces

Fibrin surfaces have been known for some time to have anticoagulant action on mammalian blood.[71,72] Liotta et al.[73] attempted to fashion a fibrin surface resembling the normal endothelium. They produced a "neointima" by utilizing a velour fabric-lined polysiloxane material throughout which fibrin deposition is encouraged to take place. This material is so constructed that the fibrin film must receive its nourishment solely from the blood stream. This serves to self-govern the growth of the film to produce what was described as a "glistening white membrane of normal endothelium." Although this material has been used to line an artificial heart device, which has been applied successfully in animals and humans, it has been noted that some clotting has occurred even when the patients were heparinized.[73,74] In addition, it has been pointed out that growth of an intima can have adverse effects on the properties of an implant and may change its physical characteristics.[3]

The Vascular Surface

There is little information available concerning the surface characteristics of the vascular system. Moolten et al.[75] have shown that normal endothelium behaves like a non-wettable surface, but that a slight disturbance, too small to be seen histologically, may cause the surface to become relatively more wettable, due to the exposure of collagenous tissue,[7] and thus serve as the locus of origin of a thrombus. The endothelium is hydrophilic,[76] but the wettability of a live surface may be a parameter with limited meaning,[77] since even mild injury of the endothelium can liberate adenosine diphosphate and cause adhesion of platelets.[78] Thus, attempts to measure surface characteristics may be obscured by platelet deposition.

There have also been a few studies reported which deal with the charge effects of vascular surfaces. Sawyer et al.[14] have reported a net charge of −3 to −13 mV on intima. Harshaw et al.[79] found that canine aorta has a net negative surface and pore charge. The density of this charge on the average is 0.5 e.s.u./cm.^{2} The charge density of the canine vena cava is slightly less than the aorta, but on a unit weight basis of tissue, the former has a greater net charge density. As part of the latter study, Harshaw et al. investigated the ionic atmosphere which surrounds the surface of the endothelium and, by using the technique of ion elution, made observations regarding the adsorption property of the blood vessel. They studied Na^+, Ca^{++}, and Cl^- and found the positive ions were more concentrated than the negative ions, as would be expected on a negatively-charged surface. The tissues containing more endothelium per gram of tissue showed a higher concentrating ability. Thus, the vena cava concentrated in the diffuse double layer surrounding its fibers about seven times more sodium ions, five times more calcium ions, and three times more chloride ions, than in the free solution. They found, further, that the Ca^{++} ions at the surface or within the tissue showed a peculiar phenomenon — self-exchange—which was interpreted as evidence for the existence of specific binding sites for calcium.[80] Work by Sawyer[15,81,82] suggests that the blood vessel wall tends to have a large number of pores in parallel series traversing the wall with a structure somewhat analogous to Swiss cheese.

Summary

In summary, we have surveyed the literature pertaining principally to the polymer aspects of nonthrombogenic surfaces. Until suitable polymers can be synthesized, heparinized polymers will undoubtedly continue to be used for clinical work. The question which has not been answered in these discussions is: what is the mechanism by which a surface is rendered nonthrombogenic? This is discussed in a later article. However, it can be noted here that, according to the widely-accepted waterfall hypothesis of intrinsic blood coagulation, a foreign surface causes activation of the so-called Hageman factor, initiating a series of enzymatic reactions which ultimately result in formation of a clot. Heparin is known to inhibit the sequence of enzymatic reactions.

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See Clinical Considerations section on last page...

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Urinary Tract Infections (due to susceptible strains of gram-negative bacteria)†	0.8-1.2 mg./kg. for 7-10 days	Larger doses or additional antibacterial therapy should be considered in severe urinary tract infections or in resistant cases involving the renal parenchyma or anatomic anomaly.	up to 5 mg./kg.
Other Infections including bacteremia, infected surgical wounds, severe soft tissue infections, and respiratory tract infections (due to susceptible strains of gram-negative bacteria)	3 mg./kg. for 7-10 days		

†Alkalinization of the urine may be a useful therapeutic adjunct.

Patients with Impaired Renal Function

To minimize the risk of ototoxicity in patients with impaired kidney function, only the first dose should be that normally recommended. Each subsequent dose should be half or less of that recommended for patients with normal renal function, depending upon the degree of renal impairment.

In patients with renal failure who are undergoing 14-hour hemodialysis twice weekly, administration of 1 mg./kg. GARAMYCIN Injectable at the end of each dialysis period has been suggested.

Clinical Considerations

Indications: GARAMYCIN Injectable is clinically effective in infections due to susceptible strains of gram-negative bacteria, including *Pseudomonas aeruginosa,* and species of indole-positive and indole-negative *Proteus, Escherichia coli,* and *Klebsiella-Aerobacter.* Bacteriologic studies should be conducted to identify the causative organism and to determine its sensitivity to gentamicin sulfate. Sensitivity discs of the drug are available for this purpose. If the susceptibility tests indicate that the causative organism is resistant to gentamicin sulfate, other appropriate antibiotic therapy should be instituted.

IN VITRO INHIBITION OF CLINICALLY IMPORTANT BACTERIA BY GENTAMICIN SULFATE (TUBE DILUTION STUDIES)

BACTERIA	No. of Strains Tested	No. of Strains (%) Inhibited by: 4 mcg./cc. or less		8 mcg./cc. or less*		No. of *In Vitro* Studies
Staphylococcus aureus	1,210	1,200	(99%)	1,206	(99%)	11
Pseudomonas aeruginosa	885	771	(87%)	828	(93%)	16
Escherichia coli	836	736	(88%)	779	(93%)	11
Indole-positive and indole-negative *Proteus* species	477	210	(44%)	358	(75%)	12
Klebsiella-Aerobacter species	292	205	(70%)	231	(79%)	10

*Number of strains (%) of gram-negative bacteria inhibited by 10 mcg./cc. or less are as follows: *Pseudomonas aeruginosa,* 828 (93%); *Escherichia coli,* 792 (95%); *Proteus* species, 393 (82%); *Klebsiella-Aerobacter* species, 284 (97%). From same studies as above.
Source: Package Insert

This drug should be limited to the treatment of serious infections caused by gram-negative bacteria, particularly *Pseudomonas aeruginosa, Proteus* and other susceptible organisms, with due regard for relative antibiotic toxicity. Therefore, the drug should be considered for use against gram-negative: 1. Bacteremia; 2. Infected surgical wounds; 3. Severe soft tissue infections, including burns complicated by sepsis; 4. Respiratory tract infections; and 5. Selected cases of urinary tract infection.

Contraindications: GARAMYCIN Injectable is contraindicated in individuals with a history of hypersensitivity or toxic reactions to gentamicin.

Warnings: Patients receiving treatment with GARAMYCIN should be under close clinical observation because of the toxicity associated with the use of this drug. Ototoxicity, vestibular and auditory, can occur in patients, primarily those with pre-existing renal damage, treated with GARAMYCIN Injectable, usually for longer periods or with higher doses than recommended.

GARAMYCIN Injectable is potentially nephrotoxic, and this should be kept in mind when it is used in patients with pre-existing renal impairment. Kidney function diminished by infection of the upper urinary tract may, however, improve during effective treatment with GARAMYCIN Injectable.

Concurrent administration of potentially ototoxic drugs such as streptomycin and kanamycin or of potentially nephrotoxic drugs such as polymyxin, colistin, and kanamycin with gentamicin sulfate has not been shown to afford any clinical advantages and, moreover may result in additive toxicity. Monitoring of vestibular, cochlear, and renal function will provide guidance for therapy in such cases.

Precautions: In patients with impaired renal function in whom serious infection develops, serum concentrations of the drug may rise, with consequently increased risk of ototoxicity. In these patients or in those in whom recommended dosage or duration of therapy must be exceeded as a life-saving measure, routine studies of kidney function should be performed when possible. These may be supplemented by evaluation of the vestibular and auditory function and measurement of serum concentration of the drug when feasible. Serum concentrations of gentamicin should be maintained below the range of 10-12 mcg./ml. to reduce risk of ototoxicity.

Ordinarily, treatment should not be given for more than 7 to 10 days or be repeated unless required for serious infection not responsive to other agents.

As with other antibiotics, treatment with GARAMYCIN Injectable may occasionally result in overgrowth of nonsensitive organisms. If superinfection occurs, appropriate therapy is indicated.

Safety for use in pregnancy or the potential for fetal ototoxicity or nephrotoxicity have not been established. Studies in pregnant animals have not revealed teratogenic or ototoxic effects in the fetus. GARAMYCIN Injectable should not be used in pregnant patients or in women of childbearing age unless its use is deemed advisable by the physician.

Adverse Reactions: The overall incidence of ototoxicity considered related to treatment with GARAMYCIN Injectable was 2.8 per cent (16 of 565 patients). Contributory factors (two or more factors were relevant to most patients) were as follows: 10 had azotemia, 10 received a total of 1 gram or more of the drug, 7 had recently received other potentially ototoxic antibiotics (streptomycin or kanamycin), and 5 were over 60 years of age. Six also had decreased high-tone hearing acuity, which returned to or toward normal in the 4 patients retested.

Analysis of BUN data indicated that 4 (2%) of 172 patients showed increases in BUN that were probably related to treatment with GARAMYCIN Injectable. Of 20 increases probably or possibly related to treatment, 7 were reversible, 9 occurred in terminal patients, and 4 had no follow-up.

Other adverse reactions associated with treatment were one instance each of urticaria, decreased hematocrit, and reversible depression of granulocytes with normal bone marrow. Other rarely reported and possibly treatment-related adverse reactions were anemia, increased reticulocyte count, rash, purpura, drug fever, hypotension, convulsions, twitching, salivation, nausea, vomiting, increased transaminase activity (SGOT or SGPT), increased serum bilirubin, decreased serum calcium, and joint pain.

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The Viewing Box

Retropharyngeal Hematomas

Two patients, both with retropharyngeal hematomas, incurred this infrequently seen lesion as a result of trauma. The first, a 16-year-old boy (Figure 1), died instantaneously of multiple injuries. A second, an 85-year-old male (Figure 2), fell out of bed and presented in the Emergency Room as an acute respiratory problem with a possible superior venacaval syndrome.

What are the Diagnoses?

Case 1

Although this teenager sustained mortal injuries to his chest, he also incurred a fracture-dislocation between the occiput and first cervical vertebra. The large retropharyngeal hematoma apparent on x-ray (Figure 1, arrows) resulted from massive bleeding. The hematoma extends from the foramen magnum to the mediastinum and includes both the retropharyngeal space in the region of the second cervical vertebra as well as the retrotracheal space, often measured at the inferior aspect of the sixth cervical vertebra to the posterior aspect of the trachea. More faithful representation of the original x-ray would reveal a distorted relationship between the tip of the odontoid process to the basion (anterior lip of the foramen magnum) and to the anterior arch of the atlas.[1]

Case 2

A large retropharyngeal and retrotracheal hematoma (Figure 2, arrows) prevented intubation of an elderly male patient by regular means, though eventually a pediatric endotracheal tube was successfully placed within the larynx. The diagnosis of a dissecting aneurysm of the aortic arch could



Figure 1



Figure 2

not be confirmed initially because of the hesitancy of the patient's family to have any diagnostic or surgical procedures performed. Using the method of conservative management of dissecting aneurysms suggested by Wheat et al.[2], the patient was placed on a regimen including Arphonad (trimethorphan) and reserpine. Several days following tracheotomy and subsequent to the patient's gradual improvement, arteriographic studies confirmed the presence of a dissecting aneurysm. However, two weeks later the patient developed a massive upper gastrointestinal hemorrhage, which, when coupled with a marked arrhythmia led to his demise. (This was felt to be a complication of reserpine therapy.) At postmortem examination the exact location of the initial rupture could not be obtained. However, the hematoma extended cephalad to the foramen magnum and caudally into the mediastinum and distal para-aortic region of the thorax.

Comment

As pointed out by Wholey et al. of the Mayo Clinic[1], based upon their series of 600 lateral cervical roentgenograms, a retropharyngeal space of more than 7 mm. or a retrotracheal space of more than 22 mm. must be considered abnormal and dictate a complete diagnostic workup. Lateral cervical roentgenograms of the neck must be reviewed for soft tissue pathology in addition to the usual review of bony pathology.

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A man of sixty who had been a grumbler all of his life, had long made a practice of changing his physician at the slightest provocation. One day he called in a young doctor who had gained a considerable reputation.

He was telling the doctor what he thought was the matter with him, when the young M.D. ventured to disagree with him.

"I beg your pardon," said the patient, "it isn't for a young man like you to disagree with an old, experienced invalid like me!"*

*Braude's Speaker's Encyclopedia.

Socialized Medicine

Jesus tried an experiment in Socialized Medicine, when He healed the ten lepers. But He never engaged in such group medical practice again! For only ONE of those ten lepers even said "Thank You." And none of them offered Christ a free meal or even a sandwich!*

*Dr. George Crane: The Quotable Dr. Crane, 1968.

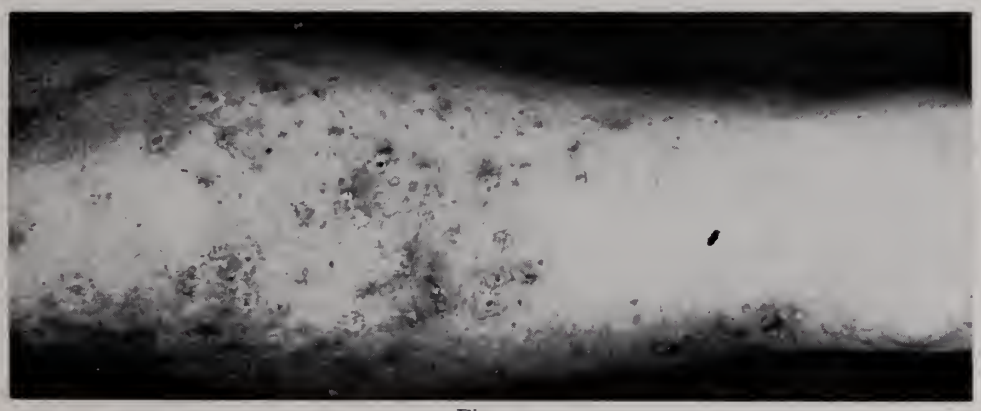
The little bees are more industrious than the big ones; gaudy and showy bees, like gaudy and showy women, are good for nothing. —Aristotle (384-322 B.C.)

Dermatology

Occupational Acne

Acne-form eruptions may be externally caused through contact with oils and various chemicals. It is a common form of occupational contact dermatitis. Chloracne is the term used when one of the chlorinated hydrocarbons is responsible; otherwise it is simply called oil acne. The following substances can give rise to this dermatitis: cutting oils (machinists), crude petroleum (refiners), coal and petroleum tars (roofers and road makers), chlornaphthalenes, chlordiphenyls, chlordiphenyloxides (electrical workers), and chlorbenzols or phenols (chemical workers). Cutting oils account for the largest number of cases. These oils consist of a petroleum base with additives such as sulfur and chlorinated compounds.

The mechanism by which these substances cause the acne-form eruption is interesting. Experimental work has demonstrated that these chemicals promote a squamous metaplasia of the sebaceous gland. In addition, there results a hyperplasia of the cells in the hair follicles. Proliferation of the epidermal cells in the sebaceous gland occurs, but differentiation fails to take place, with the result that only keratin is produced. This gives rise to the keratin plug which characterizes the primary lesion in this condition. When and if these keratinized follicles become infected a resemblance to acne vulgaris results. It should be noted that in acne of puberty sebaceous gland hyperplasia occurs; in oil acne there is a loss of sebaceous tissue. Therefore, two different pathophysiologic mechanisms result in a similar clinical picture. As might be expected, acne vulgaris is usually aggravated by contact with these substances.



Figure

Clinically it usually takes a month or more of exposure for development of the eruption. Those areas in direct contact are most commonly affected, usually the hands and arms first. However, with impregnation of the clothing the chest, abdomen, and thighs become involved. The lesions are comedones and non-inflammatory papules. Infection may occur and the lesions then resemble the pustule of acne vulgaris.

In diagnosis, age of the patient, atypical locations, and the history of contact all help differentiate oil acne from acne vulgaris. Treatment involves cleanliness of skin and clothing. The lesions resolve once contact is eliminated. In these patients response to current acne vulgaris therapy is often disappointing. Therefore, treatment consists chiefly of preventive measures.

Willard C. Peterson, Jr., M.D.
Minneapolis, Minnesota



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Case Report

Treatment of Arteria Lusoria Sinistra in the Adult

BERNARD W. THOMPSON, M.D., F.C.C.P.* AND RAYMOND C. READ, M.D., F.A.C.S.†

HUNAULD[1] IN 1753 was the first to recognize that an anomalous right subclavian artery passing behind the esophagus could cause difficulty in swallowing and lead to respiratory embarrassment.

Fioratti and Aglietti[2] in 1763 recognized a right aortic arch in the cadaver. In 1794 Bayford[3] described the symptoms related to the retro-esophageal subclavian artery and coined the term lusoria (jest of nature). Mohr[4] in 1913 diagnosed right aortic arch by roentgenogram, confirming it at necroscopy. In 1926 Jex-Blake[5] suggested that vascular rings might be amenable to surgical correction, a procedure first accomplished by Gross[6] in 1945 when he ligated and divided an anomalous right subclavian artery. This has now become standard procedure for dysphagia lusoria. In older patients, division of such a major vessel may impair blood flow to the arm, thus interfering with livelihood. Further, whenever the subclavian artery is divided, the stage is set for the development of a steal syndrome. Obviously the ideal operation includes reconstitution of subclavian blood flow, as reported in three patients with a normal arch.[7,8,9]

The purpose of the present report is to describe for the first time such a procedure in a case of right aortic arch with anomalous left subclavian artery. The term "arteria lusoria sinistra" is used when the left subclavian artery originates from the distal right aortic arch and passes behind the esophagus.[10] The vascular ring is usually completed, as in our case, by a ligamentum arteriosus connecting to the left pulmonary artery.

Case Report

A 32-year-old white male was admitted to the Veterans Administration Hospital, Little Rock, Arkansas, on January 3, 1969, complaining of dysphagia. He stated that for three years he had had difficulty swallowing and that this had recently become severe. He could drink and take soft foods, but when he ate bread or meat it stuck beneath the manubrium sterni and regurgitated. During the preceding few months he had lived on puree. Despite these symptoms he had not lost weight. While in the Air Force he had carried a diagnosis of globus hystericus.

Physical Findings

The patient showed ocular hypertelorism,‡ anti-mongoloid slant of the eyes, cleft palate and cleft lip. There was no enlargement of the heart, no murmurs were heard, and the remainder of the physical examination was non-contributory. Routine laboratory data were within normal limits. A chest film showed a right aortic arch. An esophagram (Figure 1) demonstrated a posterior indentation in the upper third of the esophagus felt to be due to extrinsic pressure from an aberrant subclavian artery associated with the right-sided aorta. Further in-



Fig. 1—Esophagram showing indentation due to aberrant left subclavian artery passing posteriorly.

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‡See Test Your Word Score, page 869.

vestigation with cine studies revealed the impression to be too large for a single subclavian artery and that it probably represented a pseudodiverticulum of the aorta. Retrograde aortography (Figure 2) outlined the right aortic arch, with separate origins of the right carotid, right subclavian, left carotid, and left subclavian arteries. The left subclavian artery arose as the fourth branch from the distal aortic arch and passed posterior to the esophagus. Esophagoscopy demonstrated anterior deviation with pulsation on the posterior aspect of the esophagus in its upper third.

Operative Findings and Procedure

On February 6, 1969, under general endotracheal anesthesia, a left posterolateral thoracotomy was done. Enlarged lymph nodes lay alongside and attached to the trachea and esophagus. These were excised and reported on frozen section to be granulomatous. The left subclavian artery (Figures 3 and 4) arose posterior to the esophagus and ascended to the apex of the left hemithorax and thence to the upper extremity. This vessel had its origin from a large pseudodiverticulum on the medial wall of the descending aorta. Also arising from this vestige of a left arch and extending to the left pulmonary artery was a long (5 cm.) ligamentum arteriosum. After mobilization of the aorta, it was noted that the entire descending aorta as far as the diaphragm lay to the right of the vertebral column. The ligamentum arteriosum was ligated and excised. This, however, did not completely free the esophagus and allow the aorta to swing posteriorly away from this organ. A vascular clamp was therefore passed across the base of the pseudodiverticulum and this divided, the proximal end being oversewn with a continuous 0000 Tevdek suture.

The left common carotid artery was then identified lying



Fig. 2—Subtraction aortogram demonstrating four separate branches off the arch of the aorta, the last being the aberrant left subclavian artery.



Fig. 3—Photograph showing the pseudodiverticulum giving rise to the aberrant left subclavian artery and long ligamentum arteriosum. The left common carotid artery passes to the right of the esophagus and trachea.

anterior and to the right of the trachea and esophagus. After this vessel was mobilized and occluded with umbilical tapes, the distal end of the left subclavian artery was anastomosed to it in an end-to-side manner, anterior to the trachea, with quadrant 0000 Tevdek sutures. The patient's postoperative course was uneventful. The radial pulses as well as the blood pressure in both upper extremities remained equal. Postoperatively the esophagram showed normal transit of the barium without identation. The patient has no difficulty swallowing solid foods and has gained ten pounds in the three months since surgery.

Discussion

The incidence of aberrant right subclavian artery with a normal left arch is estimated to be 0.6%.[11] Other forms of vascular ring are also rare. Most manifest themselves in childhood. Operation is necessary to prevent death from respiratory complications. Although aberrant right subclavian artery is diagnosed more frequently in the adult, in only a few instances have symptoms become severe enough to necessitate surgical intervention. There are only a few reports of arteria lusoria sinistra in the adult. Two have been operated on, but the details are scanty.[10,12]

It is interesting to speculate why symptoms can, as in our case, appear late in adult life. This has been explained as due to arteriosclerotic dilatation.[13] Perhaps loss of mobility of the involved structures with advancing age contributes. The aberrant subclavian artery, tautly stretched behind the esophagus, may then more readily interfere with the peristaltic wave, producing hesitancy in swallowing. In addition, the pseudodiverticulum may enlarge later in life. In the present case hypertrophied granulomatous lymph nodes encroached on the posterior aspect of the esophagus, further tightening the ring.

The classic classification of aortic vascular anomalies given by Edwards[14] is excellent in that it provides an anatomical as well as embryological basis for understanding the numerous variations. Unfortunately, it is cumbersome. When dealing with right aortic arch anomalies, the classification of Felson[12] is better, although it does not explain all the embryology. Felson[12] divided the right aortic arches into two types. In Type I, the right aortic arch passes anterior to the trachea and esophagus. The branches of the aorta are a mirror image of those normally seen. This type is frequently associated with congenital heart disease. In Type II, the aortic arch passes posterior to the trachea and esophagus, as in the case presented, which verified the findings of Felson[12] in that there was an isolated type of right-sided aortic arch without congenital heart disease. In addition, as he has further noted, the descending aorta lies to the right of the vertebral column as far distally as the diaphragm. This patient likewise shows four branches of the aortic

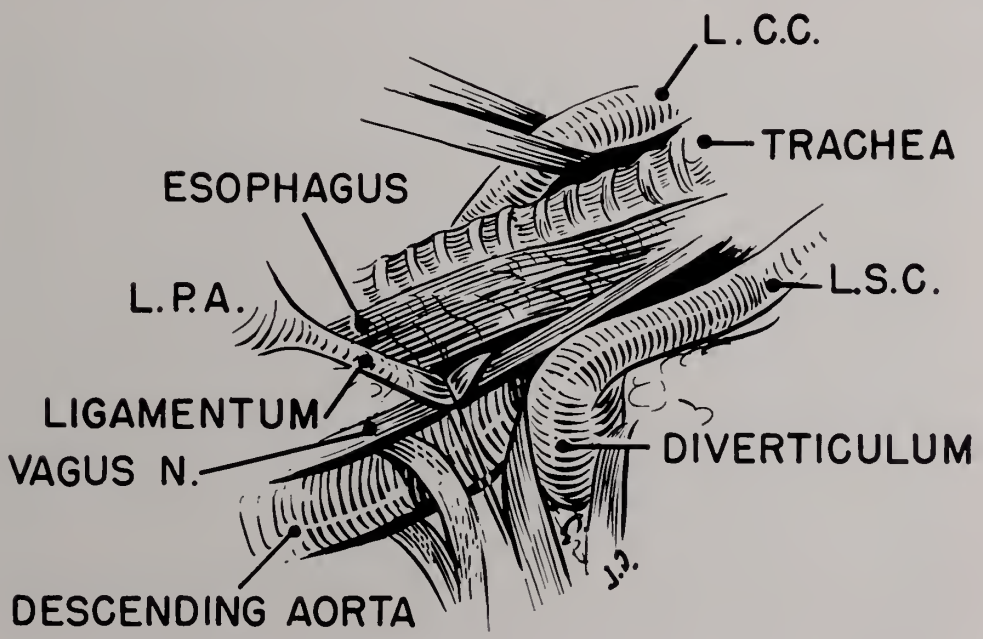


Fig. 4—Artist's concept of photograph: L.C.C.—Left common carotid artery, L.S.C.—Left subclavian artery, L.P.A.—Left pulmonary artery.

arch instead of the usual three. This has previously been reported by Robicsek[10] in seven of his 11 cases.

Our patient carried a diagnosis of globus hystericus for some ten years, during which he was treated with various antispasmodics and tranquilizers. It has previously been reported by Sanger[15] that patients with dysphagia lusoria frequently fall under this same heading. They have little difficulty in swallowing liquids and frequently do not lose weight. They are often unhappy and frustrated, with unexplained chronic difficulties in swallowing. Most of them have been followed by physicians, have been given numerous medications, and are then frequently referred for psychiatric treatment.

Numerous children have been operated on for vascular rings, and most commonly treated by ligation of subclavian arteries, a procedure which can cause ischemia in all age groups. In 1964 Hallman and Cooley[16] recommended that when adults were operated on for dysphagia lusoria, consideration should be given to re-establishing pulsatile flow. C. P. Bailey[7] in 1964, McDowell[8] in 1968, and Siderys[9] in 1969 reconstituted circulation to the arm by anastomosing the right subclavian artery to either the aorta or the right common carotid artery. We are unable to find any previous case in which the rarer arteria lusoria sinistra has been treated similarly. The patient with dysphagia lusoria should be approached through a right posterolateral thoracotomy and the divided subclavian artery anastomosed to the right common carotid artery. Patients with arteria lusoria sinistra should have a similar procedure conducted from the left side.

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The Pill

The doctor in the delivery room is an old hand at it. He grabs the newborn baby by the feet and slaps him smartly across the bottom. Then, a startling thing happens. Instead of crying, the baby starts to laugh. He laughs and laughs and laughs. The doctors and nurses are astounded. They examine the infant and see that one tiny hand is clenched into a tight fist. They pry the fingers open and as they do, the infant starts to laugh again. Clenched in its small hand is a little pill.

*Mark Wachs

A New Era

It has been suggested that historians may refer to the present age as the Age of Chiselry.*

*Maxwell Droke: The Speaker's Handbook of Humor.



Fracture Conference

The Weight-Bearing Cast in Fractures of the Tibia*

Dr. Immanuel Benjamin:

Case 1 is that of a 58-year-old nurse who was involved in a severe automobile accident on December 31, 1967. Hospitalized in Missouri in critical condition, she was given multiple transfusions until her status stabilized. She was then transferred to Rochester Methodist Hospital on January 11, 1968, where evaluation revealed fractures of all extremities: a closed transverse fracture of the lower third of the left tibia and fibula, a closed fracture of the left radius and ulna, an undisplaced fracture of the distal third of the right ulna, and an intertrochanteric fracture of the right hip.

Fracture Conference, May 6, 1968.

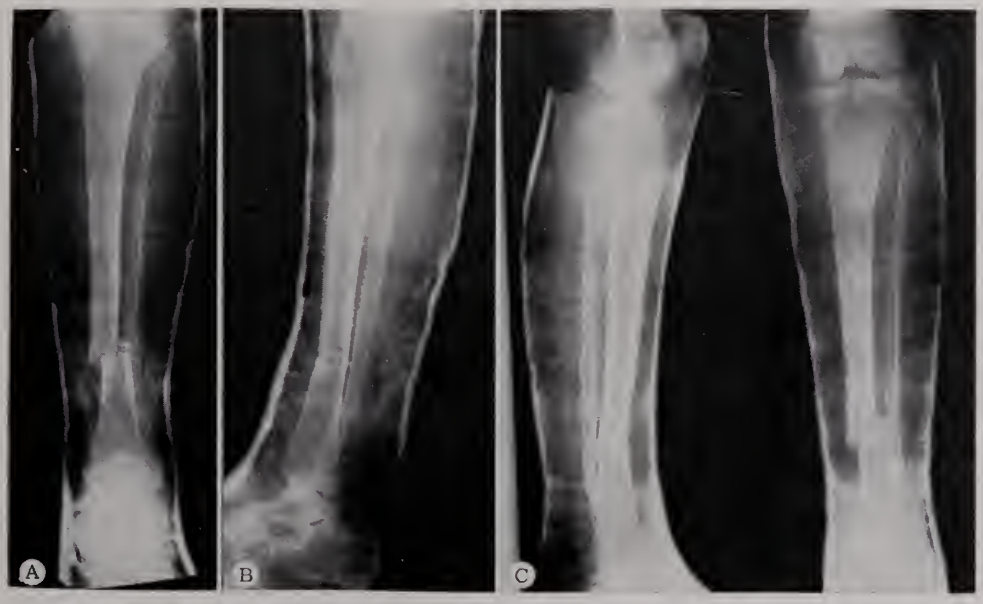


Fig. 1—Fracture left tibia three weeks after injury. *(A)* Anteroposterior view; *(B)* lateral view. *(C)* Lateral and anteroposterior views of left leg three months after injury. Notice the short-leg, patellar tendon-bearing cast.

Dr. Stanley R. Payne:

On admission she was in a long leg cast and had x-rays with her that showed adequate reduction of the left tibia. About 10 days later further x-rays were taken: Figure 1 (A) and (B). She was in fair condition when admitted, stable, perhaps in need of a little more blood, but that's about it. She had been in good health up to the time of the accident. Dr. Fisher, would you tell us how you would go about treating this patient, not necessarily concentrating initially on the tibial fracture, and whether or not you think you would be able to get her up and ambulating before all of her fractures healed?

Dr. Fisher:

She came, I assume, with a cast on the left upper extremity as well as the long leg cast on the left lower extremity. Insofar as the tibial fracture is concerned, I would be well satisfied with the position as I see it both in the lateral and in the anteroposterior views. I would be satisfied with the position of this fracture. It is "on" fairly well; at least 50% is shown in the anteroposterior view, and the lateral view seems to show 100% apposition. I think the plane of the distal tibia is acceptable with the long axis of the tibia. What she would need first would probably be internal fixation of the comminuted trochanteric fracture of her right femur.

Dr. Payne:

I didn't show the other x-rays because I want to talk briefly about tibial fractures first and show several tibial fractures in review. I want to present the total case because I found it to be an interesting one.

We went about caring for this patient as Dr. Fisher suggested. First we put her on the table and pinned her hip fracture with a McLaughlin apparatus. Next we opened her left forearm and put a compression plate on the radius and a Rush pin up the ulna. The right forearm, which had the undisplaced fracture of the ulna, was merely splinted with a single ulnar plaster splint and held in place with a conforming bandage. I did not try to treat it for the following two reasons: (1) it was unstable, and (2) I wanted her to use it actively in my plans to get her ambulating.

The forearm was placed in a long arm cast. Next we worked on the tibia and left her in the long leg cast. On February 6, we put her in a long leg, patellar tendon-bearing cast. This was one month after the accident, and about three weeks after we had pinned her hip and both bones of the forearm had been set. We sent her to the Section of Physical Therapy to see whether ambulation could be attempted. I asked the physical therapist to allow full weight bearing on the left tibia and 30 pounds of weight bearing on the right leg and to use a platform walker so that the patient would be bearing her weight on her humerus as she tried to keep her weight off her right hip. This worked out well. We used the long leg cast for about six weeks and then changed to a short leg cast: Figure 1 (C). The cast was cut back to the popliteal area posteriorly, and anteriorly it extended about to the superior pole of the patella. This cast was put on three months after the fracture and two months after full weight bearing. The anteroposterior view shows evidence that good callus formation is beginning on the medial and lateral aspect of the patient's fracture; these views do not show much about the fibula.

The patient was able to ambulate and subsequently went home, progressing from the platform walker to platform crutches and, after about three months, to regular crutches. She was allowed to put full weight on her left forearm fractures at three months.

Next Case

Dr. Benjamin:

Case 2 is that of a 42-year-old woman who was accidentally injured when a slab of sheet rock fell from a ceiling, hitting the lower part of her left leg: Figure 2 (A) and (B).

Dr. Payne:

The patient sustained a closed oblique fracture. I am slow to be converted to some things; that's why I did not immediately use a short-leg patellar tendon-bearing cast. The patient was anesthetized and placed on the fracture table. I was concerned that with the use of a weight-bearing cast only, there would be more shortening than is desirable. Steinmann pins were drilled across the tibia above and below the fracture, and a long leg cast was applied with the knee flexed: Figure 2 (C). This cast was used for three months; but I began to feel that I should have been a little more aggressive in weight bearing. I think that it has been shown that these fractures heal more rapidly if the normal muscle tone is maintained with a certain amount of stress across the fracture site. At the end of three months I removed the cast and the lower pin; I put on a Sarmiento[1] type of patellar tendon-bearing short leg cast, deeming that the upper pin engaged in the tibia would aid in preventing shortening of the fracture. I left this cast on for about a month of weight bearing. Four months had now passed since the fracture. I removed the extra pin and used a "conventional" short-leg patellar tendon-bearing walking cast in which the patient could bear full weight, walking completely unaided: Figure 2 (D) and (E). By this time she was able to return to any type of vocation or work if she so desired and if the laws of our insurance companies would allow it.

I would like to review quickly two different series. The first is that of Dr. Sarmiento[1] from the University of Miami presented at the 1967 meeting of The American Academy of Orthopaedic Surgeons and published in the July 1967 issue of *The Journal of Bone and Joint Surgery.*

Short Leg Cast

Doctor Sarmiento presented the results in the first 100 of 180 patients treated with short leg casts. None were treated with long leg weight-bearing casts. The average healing time was 15 weeks; there were no nonunions, and the maximal shortening was 2.5 cm.

Long Leg Cast

The second series was treated at Brooke Army Hospital,[2] San Antonio. The patients were from Vietnam and were being treated in essentially the same way as Dr. Sarmiento's group with the exception of the use of a long leg cast, with the leg in full extension, if the fracture was more proximal. Surgeons at Brooke Army Hospital reported that 72% of their patients were healed within five months. That is 22 weeks as compared with 15 weeks for the Florida group; however, this may be only a difference in interpretation of when the fracture is healed. At Brooke Army Hospital the maximal

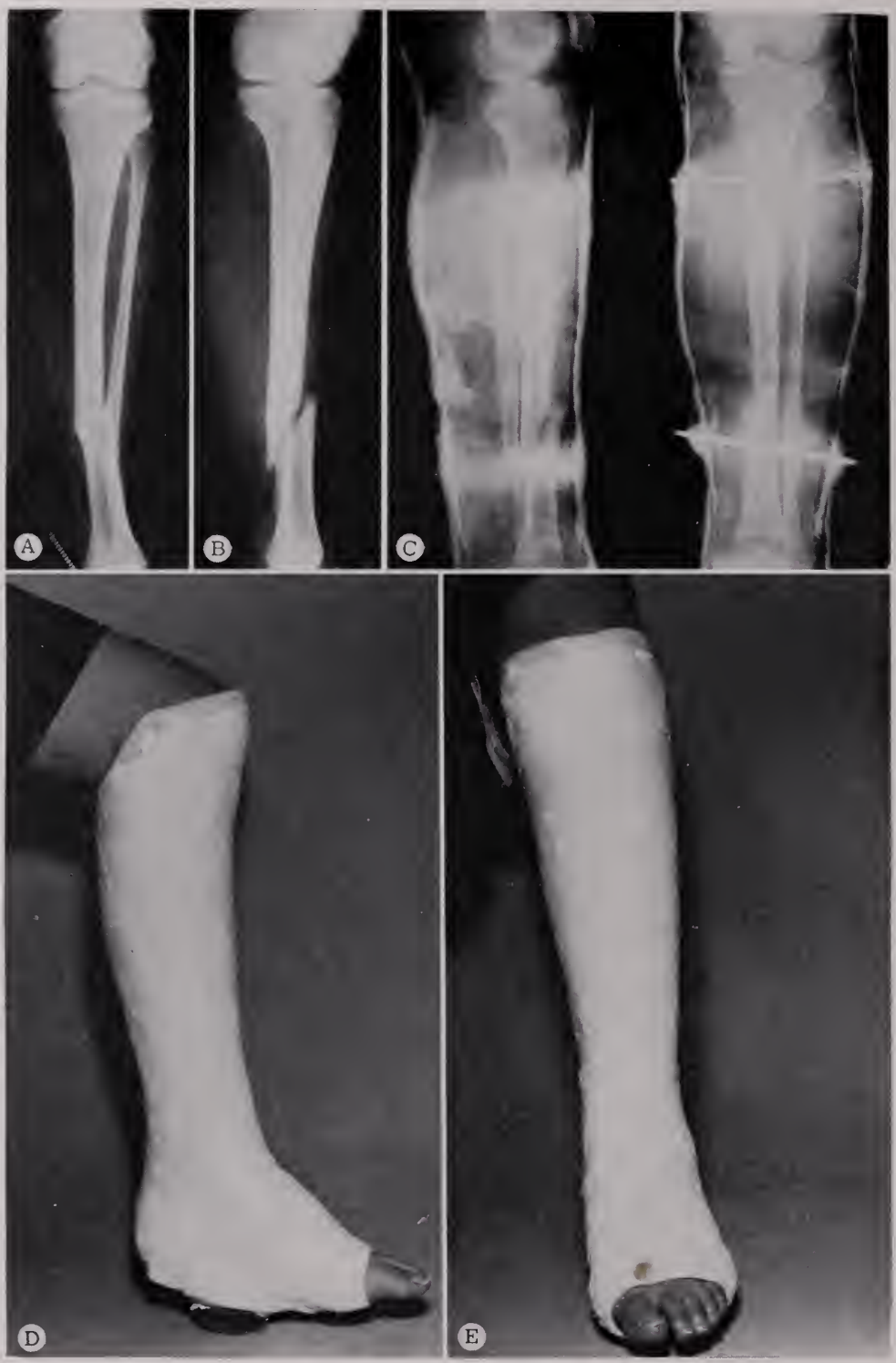


Fig. 2—Oblique fracture lower third left tibia and fibula immediately after injury. *(A)* Anteroposterior view; *(B)* lateral view. *(C)* Lateral and anteroposterior views of left leg at three months with Steinmann pins in place. *(D)* Left leg on completion of patellar tendon-bearing cast. Notice the knee flexed nearly 90° posteriorly, the cast is cut to the level of tibial plateau. Notice rubber heel. *(E)* Note proximal limit of cast at level of superior pole of patella.

shortening measured 3.3 cm, which was considered acceptable. We may say that somewhere between 1 and 1½ inches of shortening might result from the early use of a cast in this course of treatment. At the University of Miami "early" meant that the patient routinely was put in a well-padded long leg cast in bed with the leg elevated for the first seven to 10 days. After the edema subsided, the patellar tendon weight-bearing cast was applied.

Compound Fractures

The surgeons at Brooke Army Hospital[2] went into more detail. Compound fractures were well debrided. After five to six days the surgeons either did a delayed primary closure or applied a thick-split skin graft to the debrided area and put on a cast.

Weight Bearing

By weight bearing we do not necessarily mean total weight bearing. The first time the patient steps down, crutches are used; he slowly increases his weight bearing within the limits of pain he can endure without unreasonable discomfort. Of course, the threshold of pain varies from patient to patient because it is related somewhat to the type of fracture. In his published article, Dr. Sarmiento describes fractures of the full extent of the tibia. He is of the opinion that, if the cast is well molded over the medial tibial plateau and to the patellar tendons, and if it is well molded posteriorly to hold the leg forward against this area of the patellar tendon, rotational stability is fairly good. He also contends that rotational stability is increased by extending the cast over the femoral condyle, just as in a patellar tendon-bearing prosthesis for below-the-knee amputation.

Fitting the Cast

In Figure 2 (D) and (E) the recommended, trimmed-down cast is shown. It does not have to be this high over the patella, but this height over the femoral condyle is recommended; therefore I cut the cast more or less straight across from the superior pole of the patella and curved it down. Actually, it is too high posteriorly; perhaps it should be another inch lower at the level of the tibial plateau. This patient did have 90° flexion in this cast, even though it was a little high posteriorly; so I did not bring it down further, fearing that if I did so, I would weaken the hold on the femoral condyle. An effort is made to provide casts that are as light as possible so that patients will get around as soon and as easily as possible.

Technique

A week after fracture, the patient is placed on a cart in a sitting position with the injured leg hanging down. In the opinion of the surgeons at Brooke Army Hospital and of Dr. Sarmiento better alignment can be established with the leg hanging down than with an assistant holding the leg. Dr. Sarmiento applies one layer of stockinette; that is the only type of padding he uses. At Brooke Army Hospital single strips of Webril are added to the single layer of stockinette over the subcutaneous tibia, over the medial flare of the tibia, over the fibular head, over the patella, and over the malleoli. I also add single strips of Webril which afford a little more padding in the areas mentioned.

The cast is applied in sections. The first is a single four- or six-inch roll

of plaster placed around the foot and the ankle extending about three inches above the ankle. Let this set while molding it well around the malleoli and Achilles tendon, holding the ankle at an angle of 90°. This provides something to work with. The second section, a six-inch roll of plaster, is applied to the leg up to the tibial tubercule. Again it is necessary to work as hard as possible to get total contact of the cast. The prosthetist offers a helpful suggestion: that the first layer of the cast be composed of elastic plaster of paris which has been applied to an elastic mesh to make it conform easily to any contour.

The patient sits up during steps 1 and 2 but is recumbent for the next step with an assistant holding the heel with the knee flexed at about 25°. While the knee is so flexed, the knee part of the cast is applied with a four-inch roll of plaster and is molded heavily. After this, the cast is trimmed and a walking heel is applied.

Dr. Payne:

Dr. Bianco, are you using this method there? Do you modify it in any way? Just when do you use it?

Dr. Bianco:

I use this exact cast. For the unstable fractures I use pins above and below. But after six weeks if the fracture is united and the patient is up, I put him in a conventional walking cast after removal of the pins. I certainly have no argument against this method. I think the fact that some shortening develops almost proves that the full weight can not be borne on the patella in this sort of cast. In my opinion, slight shortening may be one of the advantages of this method; some shortening is associated with early healing of the fracture. Therefore I would not have left the top pin in; I would have removed it and applied this kind of cast so that the fractured bones would settle a bit. I recently attended a meeting where one man presented about half a dozen cases of tibial fractures. He used open reduction in every patient and inserted a nail-compression plate or a nail, whereas every one of the patients could have been treated very well by the method just described. The tendency now is to put in more metal, and I think we are going to get into trouble.

Dr. Payne:

Did the person you mention say anything about his average time of healing or his number of nonunions?

Dr. Bianco:

He made a big point of the fact that there was no evidence of periosteal callus on his x-rays, which proved to him that he got excellent end-to-end contact and practically Haversian-canal-to-Haversian-canal healing. He said the callus should not be palpable and that, if it can be felt, there is motion. But with good contact you do not see any evidence of callus on the roentgenograms. This is true. The method you described is adequate; I have nothing against it. Surgeons are now beginning to use open reduction and internal fixation for all tibial fractures, but many patients do not need open reduction. I think we have to use some judgment and maintain old indications for open reduction and treat most tibial fractures with closed reduction.

Dr. Southall:

I thought Dr. Sarmiento made the point that shortening did not develop

after cast application but was a matter accepted at the time of casting.

Dr. Payne:

He did make this point, and he indicated that he had ⅞-inch shortening, which was his maximal shortening. He said that only ⅜ of that ⅞ inch occurred after the cast was applied and, in his opinion, certainly not more than about ¼-inch shortening develops after the cast is applied.

Dr. Bryan:

I think that is what he said, but I am not sure that the statement is valid. I had one patient on whom I applied a skin-tight plaster; I took x-rays and checked him in one week and found he had shortened one inch. So I took him back to the operating room and remanipulated and recasted him.

Dr. Payne:

I cannot see how perfect length can be achieved by this method unless a pin is inserted across the upper segment and no shortening is expected. As Dr. Bianco said, some shortening may be valuable. On the other hand, if shortening develops it may be because this cast is around the malleoli and when the patient lifts his casted leg, he has two areas of support suspending the cast: one at the flare of the gastrocnemius posteriorly, and the other at the flare of the malleoli below to support the cast. I wonder if we are not getting a little motion on the fracture site in the pure cast with no pins. I should think it would be very difficult to put this cast on as Dr. Sarmiento says and have no shortening whatsoever.

Dr. Bryan:

In most cases this is true, but not always. In some cases, shortening follows casting. In the series mentioned, the average accepted shortening was originally ⅝ inch. However, in some cases, shortening was more than that.

Dr. Payne:

Thank you very much for your comments. These cases illustrate a method of treatment for fractures of the tibia in which partial weight bearing is allowed one week after fracture. Weight bearing is slowly and steadily increased until, within a few weeks, total weight bearing is often possible. Ideally the tibial fracture should have some inherent stability, although those who have become proficient in this method have used it in an increasing variety of tibial fractures. The method demands attention to detail and also produces some loss of length. However, the rate of union is far better than that achieved by most other methods; so perhaps some loss of length is justifiable. Surely the method deserves consideration, and you will find the articles mentioned of real interest. All in all, it is a challenging concept in fracture care.

Stanley R. Payne, M.D.*
Immanuel Benjamin, M.D.*
Einer W. Johnson, Jr., M.D.*

*Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

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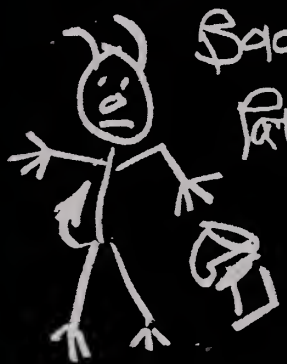


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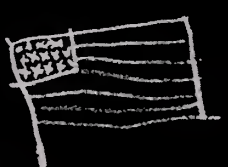
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Alcoholism

Alcohol-Related Highway Accidents

A Hospital Survey

JEROME R. HANSON, M.D.* and JOHN N. SIMONS, M.D.†

AUTOMOBILE MANUFACTURERS have been criticized recently for their emphasis on styling and their apparent lack of interest in the safety of automobile passengers. The efforts of individual crusaders and concerned politicians have resulted in increasing pressure for automobile safety standards.[1] A new Federal agency has been created to study the problem in great detail and to outline minimal standards for the automotive industry to follow. In the United States, approximately 50,000 people per year continue to lose their lives on the highways. The American public in recent years has become increasingly more conscious of the "unsafe automobile" but has not shown the same apprehension over the skill and habits of the American driver.

Studies of the circumstances surrounding automobile accidents repeatedly note that one of the major influences in the production of highway accidents is the misuse of alcohol.[2-8] The facts concerning alcohol should therefore be brought into proper perspective in the total picture of automobile accidents. This study of automobile accidents attempts to define the role of alcohol in highway accidents in a rural-suburban area and will focus on the involvement of alcohol as related to age and sex of the driver, type of accident, total number of occupants, and time of day. Since it was not legally permissible to obtain blood from these patients for alcohol determinations, all data were based on history and obvious physical findings, which undoubtedly gave lower than actual rates for alcohol use. The findings show definite patterns which are consistent with the results of previous investigators[2-4,7,9] and indicate the need for further study of the problem in the state of Minnesota.

*Mayo Graduate School of Medicine (University of Minnesota), Rochester: Resident in Plastic Surgery.
†Mayo Clinic and Mayo Foundation: Section of Plastic Surgery.

Material and Methods

The study group comprised 132 consecutive hospital admissions resulting from 106 accidents during the period July 1966 through April 1967. Eighty per cent of the accident victims were from the 11-county area in southeastern Minnesota served by the District Highway Patrol which has its headquarters in Rochester. Two thirds of the accidents occurred in Olmsted County. More than half of the patients were in the emergency room within one hour after the accident, and fewer than one third were seen by a local physician prior to their arrival in the emergency room.

The criteria for inclusion in the study follow: (1) only automobile and truck accidents were included (thus eliminating pedestrian, tractor, bicycle, or motorcycle accidents); (2) the time interval between the accident and admission to the emergency room was no greater than 24 hours; and (3) only those patients who were seen in the emergency room of one hospital and subsequently were admitted to the hospital were eligible for this study.

Information was obtained by interview with patients, passengers, and relatives, from observations by the officer at the accident scene, and from notations by emergency-room physicians. When possible, the involved automobiles were examined.

Results and Discussion

Incidence of Alcohol Consumption

One hundred ten drivers were evaluated for alcohol consumption (Table 1). The following groups were defined: (1) 59 (54%) drivers who denied the use of alcohol and presented no evidence suggesting the use of alcohol; (2) 19 (17%) drivers who admitted to heavy alcohol consumption or were obviously intoxicated at the time of admission; (3) 17 (15%) drivers who admitted to some alcohol consumption or presented evidence strongly suggesting that alcohol was an influential factor in the accident;

and (4) 15 (14%) drivers who could be neither incriminated nor exonerated regarding the use of alcohol. Thus there were 36 drivers (33%) for whom alcohol was known to be or was probably significant in producing the accident. In 51 (46%), alcohol may have played a significant role.

TABLE I
Summary of Data According to Involvement of Alcohol

Subgroups	Involvement of alcohol			
	Yes	Unknown	No	Total
All drivers	36	15	59	110
By age: 15-29 yr.	28	13	24	65
30-49	8	2	15	25
≧50	0	0	20	20
By sex: male	33	12	40	85
female	3	3	19	25
Cars involved: one	28	7	21	56
two	8	8	38	54
One car-one occupant	14	2	9	25
Time of day: 6-12 a.m.	2	3	20	25
12-6 p.m.	1	4	21	26
6-12 p.m.	12	7	15	34
12-6 a.m.	21	1	3	25

Age Factors

Twenty-eight (43%) of the 65 drivers under the age of 30 years admitted to moderate or heavy ingestion of alcohol immediately prior to the accident. No driver over the age of 50 years could be incriminated by history or physical findings in the use of alcohol, which lends support to the findings of Brenner[4] that infrequent drinkers (usually the younger age group) have a higher accident rate than do frequent drinkers. Although the older age group may consume more alcohol, they should represent a more experienced group of drivers.[7] Motivation may also play a role in keeping the older drinking driver from becoming involved in a traffic accident.[7]

Sex of the Driver

There were 85 male drivers compared to 25 female drivers, a ratio of 3.4:1. A similar male/female ratio was observed by Campbell[10] in evaluation of ACIR records of 32,287 drivers. It is of interest to note that only 57% of the licensed drivers in Minnesota are male (which closely approximates the national average), compared to 77% male drivers in the present study. Thirty-three (39%) of the male drivers were involved in definite alcohol-related accidents, compared to three (12%) of the female drivers. The total drinking population undoubtedly includes more males than females. Another factor which may influence the ratio is that drinking women are less exposed to traffic as drivers because they are more likely either to be chauffered by a male companion or to do their drinking at home.

Single vs. Two-Car Accidents

Single-car accidents involved the use of alcohol by 28 (50%) drivers, whereas only eight (14%) of the two-car accidents were alcohol-related. In a study of single-vehicle fatal accidents in California, Luethje[11] observed that 66% of 772 drivers had blood alcohol levels of 0.10% or more. He also noted an increased incidence of alcohol involvement in the younger age group.

There was a total of 25 single-car, single-occupant accidents, representing almost a fourth of the total number of accidents. Fourteen (56%) of these were alcohol-related accidents. This group is the most difficult to study because of the lack of witnesses to the accident. The size of the group, however, warrants further efforts to define such factors as alcohol, speed, and sleep.

Drivers between the ages of 15 and 19 years were the sole occupants in only a fourth of the accidents, which would indicate that younger drivers may be more responsible when alone than when accompanied by their companions.

Time of Accident

The distribution of accidents throughout the day revealed four peaks, three of which correspond to periods of increased traffic. The first peak was between 7 and 9 a.m., the second was during the noon hour, and the third, a wide peak, included persons returning from work plus late evening traffic. The fourth and most significant peak occurred after midnight when the total number of cars on the highway is reduced. These peaks were analyzed for the number of cars, number of occupants, age of driver, and involvement of alcohol.

Two (8%) of the 25 accidents between mid-

night and 6 a.m. were single-car accidents. Only two (3%) of the 59 accidents between 6 p.m. and 6 a.m. involved drivers over the age of 50 (Table 2). The large number of exposed drivers in the younger age group in this time period is one factor, but the possible importance of inexperience in night driving should be evaluated more closely. Campbell[10] suggests that driver-training programs should concentrate more attention on behind-the-wheel instruction during night hours.

TABLE 2
Time Distribution of Accidents According to Age of Driver

Time of accident	Age of driver (yr)				Total
	15-19	20-29	30-49	Over 50	
6-12 a.m.	4	5	8	8	25
12-6 p.m.	3	9	4	10	26
6-12 p.m.	10	12	10	2	34
12-6 a.m.	13	9	3	0	25
Total	30	35	25	20	110

The majority of alcohol-related accidents occurred after midnight when the total number of cars on the highway is low. Of the 36 alcohol-related accidents, 21 (58%) took place between midnight and 6 a.m. (Table 1). Only three (12%) of the 25 accidents during this period were definitely not alcohol-related. The increased consumption of alcohol during late evening hours is obvious, and an increase in alcohol-related accidents would be expected. The disturbing feature is that, in almost all accidents during this period, the use of alcohol was involved, and more than 50% of the drivers were underage for legal consumption of alcohol in Minnesota.

Comment

Certain features of this study confirm the findings of other investigators or are expected from the general information available concerning automobile accidents. The need for further definition of the alcohol problem is readily apparent and, during the course of this study, the state of Minnesota has increased its efforts to document the role of alcohol in fatal highway accidents. Since July 1, 1967, coroners' reports are being filed with the Highway Department. Among a total of 105 specimens analyzed during a six-month period, two thirds were positive for alcohol and half of those in the positive group were above the 0.10% level of presumptive intoxication. Drivers between 25 and 34 years old had a positive blood-alcohol level in 93% of blood specimens tested.[12]

There are now 20 states with implied consent laws; the number should be no less than 50 and this would be but a beginning in the efforts to define and control the effect of the automobile-alcohol interaction. Accident survivors who are unwilling or unable to consent to blood tests remain anonymous in terms of documenting blood-alcohol levels. As the present study indicates, this group probably has as high an incidence of alcohol consumption as that noted by other investigators in fatal accidents. The time to bring etiologic factors of highway accidents into proper perspective is long overdue. The notoriety of the "unsafe automobile" has produced a temporary scapegoat in the form of the automotive industry. The percentage of mechanically-induced accidents is grossly overemphasized, and the concept of creating a "safe package" for the driver and passengers ignores the basic responsibility of the individual driver to prevent highway accidents. The Minnesota highway death rate is now at an all-time high. The so-called "rights of an individual" continue to be protected at the expense of permitting daily manslaughter in an apathetic society.

Summary

This study documents the devastating role that alcohol plays as a causative factor in automobile accidents, particularly in the youthful driver. Continued effort must be directed to produce safe drivers along with our present heavy emphasis on the production of the "safe car."

References may be secured from the author or the reprints.

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(Continued to page 912)

Historical

The Evolution of Pathology*

ARTHUR H. WELLS, M.D.†

In this presentation of the part played by the pathologist in the practice of medicine in the United States of America, I intend to show that the physicians of South Vietnam must soon choose the type of hospital laboratory they wish to assist them in the diagnosis and treatment of their patients. The present war cannot last forever and the resultant economy of this country will rapidly create a climate for greatly improved diagnostic facilities.

One cannot enter upon this subject without doing homage to the many learned physicians and scientists who, prior to 1900, established the basic knowledge, created the scientific method, and set the pace and purpose in both anatomical and clinical pathology. Among so many, one can name but a few of the most outstanding: Leonardo Da Vinci, Andreas Vesalius, Morgagni, Leeuwenhoek, Pasteur, Robert Koch, Claude Bernard, Ivan Pavlov, Virchow, Charles Darwin, Cohenheim, Calmette, Chiari, Lister, Bright, Addison, Marie Curie, Roentgen, Kekule, Laennec and John Hunter. These and many more drove a penetrating wedge through the wall of ignorance and mysticism which engulfed medicine from its beginning.

By 1900 the teaching of pathological anatomy was well established in medical schools in the United States. However, about 55 years earlier, S. D. Gross, author of a book on the subject, complained that practically none of the 55 medical schools of the country taught anatomical pathology as such even though it was an established science in Europe. Some pathology had been taught, as the teachers found it useful in their lectures on medicine and surgery.

In the mid-nineteenth century, pathological anatomy as a specific course was taught in many schools on a part-time basis by physicians primarily interested in other special fields such as anatomy, surgery, and medicine. It was not until almost the turn of the twentieth century that the subject assumed sufficient importance in our country for a small group of now famous physicians to teach pathology as their main interest. Even then, many of these men had to teach part-time in other fields, including especially bacteriology, anatomy, and public health. A few implemented their meager earnings in the practice of clinical medicine.

Within the first two decades of this century, pathological anatomy became one of the best organized and most important of the basic sciences. Full-time teachers of pathology with several residents understudying in pathology were to be found in most of the medical schools and in numerous larger hospitals of the country. Many of the early full-time professors became famous for their inspired teaching and their brilliant research, especially in the field of bacteriology. This relationship of two basic sciences led to one of our first societies in pathology, the American Association of Pathologists and Bacteriologists. To this day this organization represents most of the professors of pathologic anatomy. In recent years, their research has been shifting rapidly to intracellular pathology using the electron and fluorescent microscopes.

These early teachers of pathology carried on the tradition of their German and French postgraduate instructors of avoiding any responsibility for the clinical laboratories of their hospitals. The rather small number of laboratory tests of practical value were generally performed under the part-time supervision of the department of medicine. In later years, when many more useful tests were available, these larger medical schools found other specialty departments performing the tests of their special interests in their own departments of the hospital. This dilemma of subdivided laboratories

*Prepared for the first postgraduate course in medicine sponsored by the Faculty of Medicine of the University of Saigon and the National Order of Physicians of Saigon. See editorial, page 859.

†AMA-Voluntary Physician for Vietnam, Duluth, Minnesota.

with frequent duplication of efforts and no one primarily interested in laboratory medicine led to as many as 40 separate laboratories in one of our largest teaching institutions.

This was not the case in many of the smaller medical schools and the numerous non-university hospitals scattered throughout the country; in most of these institutions the anatomical pathologist assumed the responsibility for the performance of the laboratory services. His residents in pathology learned not only anatomical but also clinical pathology. One or the other or both of these fields of medical practice became their full-time occupation and responsibility. Their expertise in what was rapidly becoming a very complicated subject of laboratory medicine led to their teaching the subject of clinical pathology in some medical schools.

Returning to the third decade of the century, the powerful American College of Surgeons demanded that all hospitals must have an acceptable laboratory service before they would receive a publicly announced accreditation for the practice of medicine. This became a great impetus to training in clinical pathology. A few years later, in 1923, the American Society of Clinical Pathologists was founded for the purpose of promoting and teaching the new and the best in laboratory procedures. Today, there is no other organization in our country which compares in importance to this bastion of laboratory medicine.

In the first quarter of this century most physicians showed a strong tendency to belittle the information obtained from the laboratory and boasted of the importance of their clinical history and physical examination. This was, in part, due to the paucity and unreliability of practical tests and the variability of technicians who ran them. The great masses of the people of those days felt that the hospital was a place to go to die.

Shortly after the end of this period the pathologists trained in both anatomical and clinical pathology became in great demand throughout the non-university hospitals of the country. This need of pathologists has never been met to this day, in spite of increases in their numbers by 100% every 10 or 12 years.

In the fourth decade the American Medical Association declared the performance of laboratory tests to be a part of the practice of medicine and that these should be performed under the supervision of a physician. As a result the American Board of Pathology was established. This group of distinguished pathologists set the postgraduate requirements of physician training to include a one-year internship plus training in an approved laboratory for four years for combined anatomical and clinical pathology, or three years in either field alone. The first three-day examination was given in 1936. Pathologists then had an official standing as specialists in medicine, and they in turn created several gradations of technical assistants. They established and accredited the schools for training these laboratory helpers and a means of qualifying the graduates of the schools. Controls were developed for routine usage to determine the accuracy of most of the laboratory tests performed, thus exposing the pathologists and their technicians to a recording of the daily accuracy of most of the tests used in the laboratory.

There developed a long struggle by the organized chemists, the American Chemical Society, for recognition of qualification as directors of medical laboratories. The AMA and many states ruled against these chemists and other laymen running laboratories. Hospitals without pathologists, however, were permitted to have a laboratory.

With ever increasing numbers of physicians, whose reputations depended upon their performance in laboratory medicine, there developed a healthy practice of inventing entirely new tests for and new approaches to the measurements of physiological processes with improvement of the established procedures. Some new tests were pathognomonic of a disease process; many others were proof of needed life-saving therapy. Still other tests gave clear-cut evidence of the stage of a disease process and its progress. The medical literature in all fields had by this time become overwhelming to most physicians. The pathologist in non-university hospitals became an important consultant for both anatomical and clinical pathology; his laboratory soon had many departments headed by specially trained medical technologists, biochemists and microbiologists. New departments included immunohematology, blood bank, pulmonary function, tracer isotopes, vir-

ology, cytology, autoimmunology, immunofluorescence, blood coagulation, chromosome studies, and a host of important tests in special biochemistry, including serum electrolytes, hormones, enzymes, serum proteins and others. By this time, one 500-bed hospital was running on the average of 1,000 tests a day, seven days a week, and employed 40 paramedical assistants and four pathologists. The pathologists were permitted to receive extra pay from practicing their specialty outside the hospital. In one year they personally reported upon over 700 autopsies, 11,000 surgical tissues, 12,000 cervical smears, 300 bone-marrow studies and 800 frozen-section diagnoses of surgical tissues.

The pathologist plays a basic role in the postgraduate medical education program in his hospital. This mostly revolves about the tests newly developed by his laboratory and about mistakes or brilliant diagnoses found in autopsies or surgical tissues. Frequently he is in charge of the intern teaching programs. He also directs the teaching of residents in pathology and of medical technologists, and helps with laboratory aspects of nurses' training.

In some large, progressive, private medical institutions, pathologists will be found in charge of many of the departments mentioned above. This ultraspecialization in pathology has resulted in several new ultra-specialized medical societies and journals devoted to the special departments of a modern hospital laboratory.

Research in laboratory medicine has become a healthy, veritable free-for-all, no-holds-barred, may-the-best-man-win proposition. For many years to come physicians and scientists in all disciplines of medicine and allied sciences, singly and as groups, will be making new and remarkable discoveries applicable to the diagnosis and care of patients.

By 1966 there were over 5,000 Board-approved pathologists in the United States plus 2,000 to 3,000 non-approved physicians practicing pathology. Today the federal government will not pay hospitals for the care of elderly citizens on social security, unless the hospital laboratory is under the supervision of a pathologist at least one day a month for small hospitals in rural areas.

Whereas at one time, 30 years ago, many physicians minimized the need of laboratory assistance in the diagnosis and treatment of their patients, they now almost unanimously agree that knowledge of the use of the laboratory and the availability of a good one is absolutely essential to the proper care of their patients. Today the great masses of the people no longer dread entering the hospital, but demand the best possible care for their illnesses.

It is true that laboratory medicine has developed much differently in at least one well established nation. Pharmacists are generally in charge of hospital laboratories. The use of the information derived from many of these laboratories, even today, plays only a small role in the everyday practice of clinical medicine. Possibly this would compare to the usage of our laboratories in the first quarter of this century. It would seem that, at the present time, in Vietnam, there may be no alternative to leaving the responsibility of the laboratory to the pharmacists.

In conclusion, it is clear that the physicians of South Vietnam will, with cessation of the war and better economics, soon have the same choice as to how they wish to have their hospital laboratories run. Will these laboratories be under the control of: (1) individuals not trained in medical science, (2) physicians whose chief interest is the clinical care of their personal patients, or (3) physicians specially trained in the science of laboratory medicine?

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Special Article

Psychological Effects of Prisoner-of-War Experiences*

GAYLE K. LUMRY, Ph.D.†

THE PURPOSE of this paper is to review the literature available to support Dr. Leslie Caplan's thesis that all veterans who have been subjected to prisoner-of-war experiences ought to receive service-connected disability automatically. This conviction of Dr. Leslie Caplan, a Minnesota psychiatrist, stemmed from his own prisoner-of-war experiences in Germany as the only physician to provide medical care for 2600 prisoners who were forced to march 600 miles during mid-winter with inadequate clothing, practically no medical supplies, and low-quality food rations of only 800 calories a day.

Physical Effects of Psychological Stress

Such extremes of severe psychological stress and physical deprivation may leave prisoners of war with degrees of systemic disability not readily detectable in ordinary physical examinations. As continuing effects Dr. Caplan cited "inability to maintain proper weight, general nervousness, excessive sweating, visual defects, optic atrophy, hernias developed during periods of emaciation, cardiac and gastrointestinal complaints and bone defects." He also speculated that "malnutrition may influence the susceptibility to, or the course of, such important diseases as arteriosclerosis, hypertension, neoplasms, allergies, cirrhosis of the liver, peptic ulcer, and certain of the anemias," and thereby shorten the life span. He further suggested that "the tremendous strain and trauma of just staying alive under dire circumstances could theoretically exhaust the adrenal glands and may contribute to adrenal depletion later in life." He felt that the level of "general experience was sufficiently substandard in terms of nutrition, fatigue, stress, and lack of medical care as to result in permanent residuals."

Controlled Experiments

Although controlled laboratory experiments on stress and deprivation are hardly the equivalent of prisoner-of-war experiences, they are relevant to this discussion in that they emphasize how quickly the effects of stress and deprivation manifest themselves in the human organism.

In 1956 the Group for the Advancement of Psychiatry[2] reported on the experimental investigation of the various factors which might be involved in forceful indoctrination of prisoners: e.g., "brain washing" or "thought reform." In evaluating their findings, it must be recalled that the investigators were focusing on only one stress at a time; the subjects were volunteers and had every reason to believe that the experimenters were benevolently inclined toward them; also, a definite date for termination of the experiment was set.

Brozek, Keys, Schiele and others[2] conducted a series of experiments at the University of Minnesota on the consequences of a starvation diet: 1600 calories a day for six months. This diet included adequate minerals and proteins and was better than that offered in prisoner-of-war camps. Termination time was clearly indicated; every effort was made to maintain morale, and adequate living quarters were provided.

Loss of Physical Fitness

Within the six-month period the subjects lost one fourth of their body weight and demonstrated profound changes in physical fitness as well as increased irritability, depression and pronounced apathy. Complex prolonged tests of intellectual functions were difficult to perform. The shadow of the heart diminished in size and changes occurred in the electrocardiograms. Twelve months were required for com-

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See editorial, page 861.

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plete physical and psychological restitution.

Loss of Sleep

Tyler[2] studied the effects of sleep deprivation on 350 volunteers extending up to 112 hours. Between 48 to 72 hours, difficulty in thinking and perception was noticeable; by 100 hours, psychotic phases were frequently manifested.

Isolation

The literature on isolation and sensory deprivation has been well reviewed by Ruff.[3] Isolation produced generalized impairment of perception with deficits most striking in tests of visual-motor coordination, shape constancy, accuracy of tactual perception and spatial orientation. Most studies reported difficulties in maintaining goal-directed thought. Measures of reasoning and problem-solving showed deficits, while simple recall or rote learning tended not to be affected. Somesthetic changes and body-image disturbances were frequently reported along with some hallucinatory experiences. Efforts to measure affective changes have consistently demonstrated signs of discomfort and irritability to the point of anxiety panic attacks.

Effect of Stress

Also pertinent to this discussion is the work of Selye[4] on the general adaptation syndrome to stress. He postulates that, if stress is sufficiently severe and prolonged, it can cause certain changes in the structure and chemical composition of the body. These faulty adaptive reactions can encourage other difficulties such as high blood pressure, ulcers, rheumatic afflictions and cardiovascular and kidney diseases.

Man's Search for Meaning

The experiences of severe psychological stress and physical deprivation as recounted by the survivors of the internment camps are probably more relevant to the actual prisoner-of-war experience and provide a dramatic contrast to the limited experimental laboratory situation. Although many excellent accounts exist, the graphic picture presented by Viktor Frankl in *Man's Search for Meaning*[5] is particularly appropriate in understanding how such experiences could result in long-term delayed residual effects of both a psychological and a physical nature.

Musselman

Survival seemed a matter of accident; the chances were one in 20. In the camps after the initial state of shock and terror, apathy became the dominant attitude, sometimes to such an extent that the prisoner became a "musselman," a term applied to a prisoner who just gave up the struggle to live and died. Regressive behavior was universal as an adaptive mechanism since phantasy served as an outlet for aggressive reactions toward the SS. Denial of reality, as Bettelheim[6] points out, made the intolerable, tolerable. Any manifestation of individuality was punishable by death; interpersonal isolation was the rule since self-survival was the goal. Frankl states: "It is a peculiarity of man that he can live only by looking to the future,"[5] and in the CC camps even this was denied.

Concentration Camp Syndrome

The majority of survivors of the internment and prison camps displayed a syndrome which has been labelled the post-KZ syndrome or concentration-camp syndrome,[11] characterized by weight loss, emotional and autonomic lability and instability, irritability, apathy, decreased self-esteem, depressive trends and difficulty in concentrating. The long-term effects of this experience received little notice until the late 1950s when articles began to appear and probably provided the basis for the Restitution Laws enacted by the Federal Republic of West Germany. No accurate figures are available, but Bensheim[8] reports that in 1960 half of all patients in an NP clinic in Haifa were under treatment for residues of Nazi persecution. The pathologic effects were discernible not only among survivors of the camp but in persons who were in hiding or on the run.

The Concentration-Camp syndrome has been described as marked anxiety with irritability, restlessness, apprehensiveness, and a startle reaction to ordinary stimuli. Somatic involvement of almost all organ systems has been reported. Obsessive ruminative states have been noted; most victims seem to feel that nothing of real significance has happened in

their lives since these experiences. Their symptoms are very similar to those described after prolonged combat stress or by the survivors of Hiroshima. Depressive features of the Concentration-Camp syndrome seem associated not only with mourning for departed relatives and friends but also with survival guilt, which Chodoff[9] feels may be associated with the illusion that thereby murdered relatives are kept alive, or may be related to death wishes against others in this personal battle for survival.

Japanese vs. German Prison Camps

In 1954 the U.S. Government published an evaluation[10] of the experiences of prisoners of war in Japanese and German prison camps. Two groups of prisoners of approximately 2,000 each were compared with groups of veterans who had been exposed to combat only. Japanese prisoners of war averaged 38 months in prison camp with 34% dying before liberation. The European group averaged ten months in camp with only 1% dying before liberation. During the first two years after liberation the Japanese ex-prisoners of war showed a marked mortality rate and then a diminished but still excessive rate during the next four years. They also showed a wide variety of illnesses which interfered with their ability to work. The European prisoners of war showed no statistically significant differences from their combat controls in mortality rate, physical disability or inability to work. Six years later, however, the European veterans showed a relative increase in malnutrition, psychoneurosis, and gastrointestinal disorders.

Danish, French, German and Norwegian Studies

Danish researchers,[12] evaluating 1,300 surviving Danish prisoners of war, found that 75% of the ex-prisoners reported complaints similar to the KZ syndrome six years after the war. The authors found a correlation in severity of symptoms with degree of weight loss and duration of imprisonment. They comment that the etiology must, to a great extent, be conditioned by somatogenic and lesional factors.

The most intensive and exhaustive study of the prisoner of war has been carried out in Norway by Strom, Refsum, Eitinger and others[13] who were asked to evaluate Norwegian prisoners of war who had made a good recovery during the immediate post-war period and had managed to adapt themselves well over a period of years but were then showing symptoms of breakdown. Three hundred cases were examined, of which only the first 100 were reported.

Late Symptoms

At the time of the evaluation, 15 to 20 years after imprisonment, increased fatigue, impairment of memory, dysphoric mood, emotional instability, sleep impairment, feelings of insufficiency, loss of initiative, nervousness, restlessness, irritability, vertigo, vegetative lability and headache were noted in the majority of patients and appeared to be similar to the Concentration-Camp syndrome noted by the Danish investigators. This syndrome could not be related to pre-imprisonment adjustment but rather was correlated with duration and degree of severity of internment, loss of weight, head injuries and serious infectious diseases. Psychological tests indicated a definite organic pattern in 82 cases, and trends toward a deviant pattern were noted in 10 others.

Neurologic Findings

Clinical neurological findings were positive in 88 cases; positive psychiatric symptoms typical for chronic brain syndrome were found in 85 cases. A pneumoencephalogram could be performed in 89 cases; of these, three were technical failures; in 75 cases the findings were pathological. The spinal fluid was examined in 93 cases, with 29 pathological findings; of the 96 cases examined by EEG, 27 were pathological. When at least four of these independent methods demonstrated cerebral dysfunction, it was assumed that organic brain disease was more than probable. With this criterion, 90% suffered from organic brain dysfunction. From autopsy reports on malnutrition victims, Osvik, one of the co-authors, found reduction of the anterior pituitary lobe and a diminution of the heart.

Employability

In the social-medical examination of these ex-prisoners, all of them were classified as completely fit for work prior to internment. However, at the time of the examination, 35

were not working, 36 were critical with regard to continued employment, and only 29 could be said to be in temporarily satisfactory employment. Seventy-nine of the subjects appeared to have lowered work capacity before 1950, while 18 noted no reduction in capacity until after 1950. Only three felt that they were still fully capable of working. The Norwegian committee attributed the work disability to the KZ syndrome and recommended to the Norwegian government increased compensation for them.[13]

Intellectual Decline

The German Federal Veterans Administration in Cologne[11] studied the long-term results of nutritional deficiency and psychological stress in 300 former prisoners of war by means of psychological tests. One fifth of this group showed a greater decline in intellectual abilities than might be expected from the normal aging process, the greatest loss appearing in those tasks which required attentiveness and ability to learn new tasks. "In general, we can recognize a disturbance in intellectual mobility and elasticity."[11]

Psychiatric Problems

In France Raveau[11] reported the results of his examination of 466 French survivors of internment 10 to 15 years after their return from captivity. In 11% he noted neurological findings, of which 7% showed signs of epilepsy; 89% had psychiatric problems which he divided into three categories: 24% seemed to involve a "more particularly organic disorder and were characterized by premature exhaustion, residual asthenia, and premature senescence; 29% manifested neurotic conflicts related to traumatic prison experiences, and 37% showed the previous two manifestations with signs of diencephalic alterations."[11]

Studies by other participating countries, though less elaborate in design, supported the Conference conclusion that a process of premature aging, both somatic and psychic, could be well documented in former prisoners of war.

The Conference made the following recommendations: "It was their opinion that it was necessary: (1) to eliminate all legal time limits for submitting applications in connection with disability; (2) to have these persons benefit from the presumption of origin and aggravation, without time limit, which excludes any provision tending to reduce the disability rate on the grounds of the applicant's age or because of the time when the application for pension was made." Furthermore: "The conference recommended the adoption in the various countries of a system of reparations based on these principles."[11]

It is perhaps time, in line with Dr. Caplan's strongly expressed opinion, to re-evaluate the medical and vocational status of ex-prisoners of war in the United States.

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Longevity is worth having only when it is accompanied by the temperamental harmony which makes its possessor, even in extreme old age, take delight in the sheer joy of living.—Forbes Gray

Comparison of World War II, Korean, and Vietnamese Prisoners of War*

ALDEN V. HALLORAN, M.S.W.†

When we think of World War II, we think of 15,000,000 plus servicemen under arms, of whom 139,000 were taken prisoner, all but 4,000 being Army and Army-Air Force: prisoners who viewed capture as just another military engagement, who had a great unity of purpose and spirit with one goal—to survive and escape. They behaved as all Americans had in previous recorded history when deprived of their freedom, with an almost overwhelming impulse to get away. The Japanese and the Germans both wrote at some length about the most uncooperative, noisiest, most obstinate, most irreverent prisoners that they had ever tried to hold, namely the Americans. When captured, they formed tight little units of three or four, the "buddy system," until the more characteristic types of social structure could develop. We think of them as men who voluntarily united for collective strength, who respected and supported their leaders, who volunteered for unpleasant jobs for their collective well being, and who developed their own system of justice regarding prison conduct.

Treatment was inconsistent, although the Axis captors usually abided by the Geneva Convention of 1929. In most cases prisoners had adequate quarters, were allowed to recognize their leaders, could send and receive mail, and had the benefit of Red Cross medical parcels; but there were atrocities committed which precipitated the 1949 Geneva Convention, adding specific prohibitions against cruelty. Many World War II prisoners died of malnutrition. There were reports of physical brutality and coercion by German police dogs to try to secure confessions. In some cases, resistance led to forced labor in the Japanese mines; the Japanese also ordered the execution of several captured American airmen. But when severe physical treatment was used, it served to unify the prisoners in their efforts to escape and harass the enemy. In spite of extreme hardship men mustered their physical and mental resources and maintained a high esprit de corps.

Korean Prisoners of War

This was not the pattern of conduct of the Korean prisoners of war. Of 5,000,000 plus servicemen, there were some 7,000 Army and 235 Air Force prisoners, half of whom were draftees, better trained militarily and with a slightly higher educational level than their counterparts in World War II. They fell into the hands of the enemy, not because of incompetence, but because they were suddenly surrounded by such hoards of Chinese that there was no escape. Many were captured in groups of several hundred. But something was profoundly different about these prisoners. Not one escaped and got back to the lines; not one even managed to steal enough radio equipment from the Chinese to communicate with United States bases, as had been done previously.

Brainwashing Effect

Letters began coming home exhorting mothers to unite with other informed citizens to stop the senseless slaughtering of innocent civilians for the profit of the "Wall Street imperialistic warmongers." Confessions and self-incriminations written by soldiers began to appear in typical Communist terminology. Major Mayer,[1] then an Army psychiatrist, studied one thousand of these men as well as several hundred prisoners from other United Nations countries, such as the Turks and Colombians, immediately after their release. He reported that Americans would not talk to one another; they would talk only about one another—with a strange absence of affect. After they had been checked out medically, they were told that they could have a pass and go into

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See editorial, page 861.

downtown Tokyo; but only about one out of five took advantage of the opportunity after three years of confinement. Those who went on pass did so by themselves, which soldiers seldom do. When the Red Cross offered the men permission to call home free to talk with their mother, girl friend, or wife, anywhere in the United States, more than half said there was no one they wanted to call. Many admitted to having written confessions containing self-denunciations and recognition of their wrongdoing as "pawns of the imperialists." It appeared that these soldiers had been subjected to a sinisterly irresistible and coercive procedure called brainwashing. This was the first time that American prisoners were in the hands of captors who were determined not only to intern them, but to change their attitudes and philosophy. To accomplish this, their captors did not use drugs or hypnosis, nor did they force confessions; instead they employed a very effective system which indoctrinated their captives "when they got up, when they went to bed, taught them all day, and taught them on the way."[1] Familiar principles of psychology were applied to deprive them of their power of choice and their sense of responsibility, in an attempt to depreciate fundamental values and interfere with basic human relationships.

How was this accomplished? There had been reports of atrocities committed by the North Koreans in which they would line up prisoners in a trench and shoot them in the back. Thus the average soldier in the front line bunker in Korea fully expected that if he were captured, he would be spat upon, beaten, and executed. To the surprise of the prisoners the Chinese greeted them in a friendly fashion, holding out hope of humane treatment if the prisoners would cooperate. According to Schein's[2] reports, the severe material hardships of the march to the North and the primitive conditions of the temporary camps rendered the prisoners apathetic, disorganized, and demoralized.

Psychological Pressures

The prisoners were subjected to psychological rather than physical pressures. Men were divided into small groups and indoctrinated by young Chinese instructors, one to every 30 prisoners. These instructors were graduates of American universities, mostly in the social sciences, spoke English, and were familiar with American idioms, attitudes, and value systems. Wearing no uniform and carrying no weapon, one of these instructors would meet with about 12 of his new American students and give them a warm, humble, sincere welcoming speech requesting their cooperation and an open mind to learn the truth.

According to Mayer,[1] it was during this period that there appeared to be a total absence of spontaneous organization among the men. The officers were separated from the men. "It was a dog-eat-dog existence, with every man being for himself with an incomprehensible philosophy of, 'my survival is going to be my private affair, buddy, and yours is your private affair.' "[1] During this interval four out of every ten Americans captured died, the highest death rate of any American group in any type of captivity since the American Revolution. Of 7,000 men captured, only 4,000 survived. Many suffered from a disease Mayer[1] called "give-up-itis, the mother's boy syndrome, the pampered, the dependent, the inadequate kid who cried himself to sleep at night, who wouldn't eat food because it looked bad, wouldn't respond to initiative, wouldn't respond to leadership, and would bury his head in a blanket and want to be left alone." Through a system of supposed confessions, suspicion, and illusions of informers being everywhere, men were socially isolated—not in bricks and mortar, but in an emotional, solitary-confinement cell. They were prevented from receiving mail from their families; hence the expressions of love and reassurance that every man needs were not forthcoming. The only mail that was delivered were the Dear John letters, the divorce subpoenas, notices of illness in the family, or complaining letters from mother.

The 24-month education program in which the prisoners were involved was basically standard Communist material. "Before they were through, many prisoners received more hours of formal structured education than they had received in their total education in the United States."[1] Physical torture, while not employed, was a factor in inducing compliance. Lengthy interrogations, kindly but repetitive, self-criticism, and confessions to war crimes such as use of germ warfare or other "big lies" seemed to

be the principal methods of achieving compliance.

Perverse Rewards

According to Biderman[3]: "Like an animal in a skinner box, the prisoner was subjected to a pervasive system of rewards and punishment designed to produce conforming behavior." Getting a confession accepted became so paramount that when it happened, the prisoner felt relief and began to half believe the fabrications he had invented to satisfy his jailers. Through this insidious orientation and a process of material rewards, individuals were encouraged to inform on one another over insignificant things, of no military significance, with the rationalization that it was an exercise in social responsibility. In the past, both informers and those informed on would usually end up dead, but not so in the Chinese prisoner-of-war camps. A kindly young Chinese would take the man informed upon for a walking conference and impress upon him the importance of confession, and the session would end with a signed confession about some harmless act or minor infraction of camp rules. This insidious process would naturally drive wedges of antagonism among basically loyal American soldiers.

More than half of the Korean prisoners of war did nothing for which they could be criticized. Doing nothing was, in fact, their shortcoming. They were simply corralled and pushed along in this "educational" system. What happened to these men? Were they really lacking in moral fiber? Had they become so comfortable, so secure, so materialistic, so hedonistic that they didn't recognize a threat when it existed? Had they lost all loyalty and feeling of responsibility for one another? Because of this concern President Eisenhower published a military document called the Code of Conduct following the Korean War—a statement of principles by which every prisoner of war must abide, including making no oral or written statements disloyal to the United States.

Resist the Enemy

The Third Article in the Code is of interest. If ever captured, resist the enemy; don't cooperate with him. Militarily this is crucial, as we used 15,000 fully armed troops to guard the Chinese soldiers, 15,000 men who could have been used in combat. In contrast, the Chinese managed to hold one camp containing 600 Americans with as few as six armed guards.

One requirement of this document is to attempt escape. Of the 4,000 Americans who survived for over three years in captivity in Korea, not a single one ever succeeded in an engineered escape from an established prison camp. This passivity existed even though one of the new articles of the Geneva Convention of 1949 had recognized that prisoners have a duty to escape and cannot be punished, if recaptured, for offenses committed to facilitate the escape.

In less than 10 years there seemed to have developed some vast change in attitude, a new philosophy which, according to Mayer, said: "Get anything you want, get it right away, deny yourself nothing, don't discipline yourself, enjoy materialistic comfort, and rest securely."

The Vietnam Prisoner of War

Colonel William Tiffany[4] has reported that the troop morale in Vietnam is better than that of World War II or Korea. The rotation policy, the brief, intensive, and sporadic fighting alternating with periods of calm, the superb training, and the excellent preventive and psychiatric treatment programs contribute to a fine esprit de corps. Where 23% of all cases medically evacuated in World War II were psychiatric, in the Vietnam War this percentage is only 6%. According to Major Franklin Jones,[5] psychiatric consultant for the 25th Infantry Division, the psychiatric casualty rate in Vietnam from January 1965 through December 1966 was about 12 per thousand per year as compared to 37 per thousand per year in Korea. The World War II rates ranged from a high of 101 per thousand troops per year in the First Army in Europe to 28 per thousand per year in the Ninth Army. A more recently identified disorder known as the "short-timers' syndrome"[5] has appeared, characterized during the terminal weeks of fixed tours by the reaction: "If I go out there again, I'll get it for sure."

Brainwashed

Unfortunately, in view of the fact that all prisoners of war in Vietnam are treated as war criminals, without the benefit of the 1949 Gene-

va Convention, information regarding the numbers, treatment, or behavior of these men is lacking. There are some 1300 American soldiers reported missing in action, but how many of these are prisoners of war is not known. The North Vietnamese do not release the names of prisoners, or allow an exchange of mail. Very few combat troops have been taken in groups; most prisoners are pilots and air crewmen: officers rather than enlisted men. There are 500 to 600 such prisoners. Reports indicate that they are being systematically brainwashed and that, amid fanfare, some of them have been brought from secret cells, called air pirates, paraded through the streets of Hanoi, trotted through outlandish anti-American confessions and then locked up again.[6,7,8] The Hanoi regime has exhibited some of these prisoners at press conferences, where they appear drawn, haggard, bewildered, and retarded in speech and action. The Peking radio has broadcast statements attributed to identified pilots confessing to the revolting crimes of bombing the innocent people of the Democratic Republic of Vietnam. "The local people have treated me most humanely, although I am a criminal." "I have received adequate food and medical care in spite of my vicious crimes against them."

There is still room for speculation about the prisoners of war in North Vietnam. Possibly the North Vietnamese are allowing only brainwashed prisoners to be interviewed or released, which would indicate that the number who have complied may be small.

It is obvious that the World War II prisoners tolerated the stress of internment much better than their Korean counterparts. The conditions of imprisonment were much different; brainwashing as such did not exist, and the potential for resistance and escape was greater.

It may long be argued that the American prisoners of war in Korea revealed a lack of ability to tolerate stress and a lack of moral character. Both Mayer[10] and Kinkead[11] subscribe to this belief. They were partially influenced by the contrast with the Turks who were subjected to the same conditions of captivity as the Americans but resisted to the man; of 229 captured, 229 survived. They remained an intact group dependent on one another, with a positive attitude and respect for military leadership. The senior prisoner took command and the others supported him without question. On the other hand, sociologist Biderman,[3] who studied 235 Air Force prisoners, and also West[12] take exception to these views and try to justify the prisoners' behavior on the basis of excessive psychological pressures. Many were suffering from psychiatric problems and, in studies of 149 repatriated prisoners of Korea done by Segal,[13] disinterest, anxiety, psychosomatic symptoms, depression, and suspiciousness verging on paranoid thinking were found to be common post-release phenomena.

Breaking Point

According to Chodoff,[14] some collaborators had "weak egos and were unable to withstand pressure; some were opportunists, some were curious intellectuals, and some were of low status, poorly educated persons who had gotten little from the American way of life."

Wolff,[12] Hickle,[12] and West[12] agreed that even the most highly motivated men have a breaking point and will eventually succumb to isolation, interrogation, threats, degradation, and sensory deprivation. West[15] has suggested that ways to outwit the enemy, techniques for maintaining one's own integrity, and ways to sustain one's ego in the face of assault should be taught in order to raise a serviceman's threshold against brainwashing procedures.

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6-18. May be secured from the author or the reprints.

Money amassed either commands or obeys each of us.—Horace.



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Laboratory Letter

So Your Patient Has a High Alkaline Phosphatase

BUT WHAT does it mean? Bone or liver disease? A disorder elsewhere? Or is it a red herring—a falsely high value that will lead to frustration, worry, and expense? Let's take the last question first.

Red Herrings

How high is the alkaline phosphatase? If you are fishing for red herrings, you ought to drop your line in the gray waters between 85 and 125 units (normal range 30-85 units on SMA-12/60 chemistry graph). Values over 125 units generally indicate disease.

What causes a falsely positive borderline alkaline phosphatase? For one thing, a nonfasting specimen. Some serum alkaline phosphatase originates in the small intestine. After a meal, especially a fatty one, intestinal phosphatase enters the circulation by way of the thoracic duct, elevating serum levels by as much as 25 percent[1] And lipemia itself can raise results by clouding serum and interfering with colorimetric measurements.

But suppose your patient was fasting and the serum was clear and the alkaline phosphatase still inexplicably high. What then? Then you ought to consider the way the sample was handled after venapuncture. Was it allowed to sit exposed for hours to air and room temperature? Was it mailed on a Friday and left to incubate in some postal way station over a weekend or a holiday?

If so, the alkaline phosphatase could have risen by as much as 40 percent.[2] As serum stands, it gradually loses CO_2. This process results in a high pH. Heat accelerates this pH change. Though we have not systematically studied this phenomenon on the SMA-12/60, we believe it occurs. During the last three summer months, we received 87 sera (less than 2 percent of all specimens analyzed) in which glycolysis* had occurred. Glycolysis, which results in extremely low blood sugars, takes place when sera are old or exposed to summer heat. In these 87 sera, the upper limit of normal, as calculated on probability paper, was 105 units. In the other sera, with normal or high glucoses, the calculated upper limit of normal was 84 units. Thus, 87 sera exposed to summer heat had a 25-percent higher upper limit of alkaline phosphatase. So keep in mind the state of the serum when alkaline phosphatase is mysteriously high.

Drugs

But let's assume your patient was fasting and the serum was fresh and that he or she has none of the usual diseases that give rise to a high alkaline phosphatase. Could drugs be responsible? Drugs can produce a hypersensitivity cholestasis (Table 1) with average alkaline phosphatases about three times normal. Typically, patients will have low-grade fever and will complain of anorexia, nausea, and chills. About half will be jaundiced or will have pruritis, abdominal pain, or a palpable liver. And about 90 percent will have one or more of these laboratory findings: an elevated sedimentation rate, an

*See Test Your Word Score, page 869.

increased percent of eosinophils on peripheral smear, a high serum bilirubin, or an elevated serum cholesterol.[3]

TABLE 1*

Drugs Producing Cholestasis on a Hypersensitivity Basis

Frequent Offenders	Infrequent Offenders:	Others:
Chlorpromazine (Thorazine)	Promazine (Sparine)	Chlorpropamide (Diabinese)
Meparazine (Pacatal)	Chlordiazepoxide (Librium)	Methimazole (Tapazole)
Prochlorperazine (Compazine)	Sulfonamides	Tobutamide (Orinase)
Trifluoperazine (Stelazine)	Para-aminosalicylic acid	Thiazide Diuretics
	Erythromycin estolate (Erythromycin)	(Diurel and others)

*Table modified from Iber, F. L., Postgraduate Medicine, pages 30 to 38, January, 1967.

True High Alkaline Phosphatases

Now to the nitty gritty. Suppose the alkaline phosphatase elevation is real, i.e., disease causes it. How do you go about ferreting out the culprit? That depends on your turn of mind. Personally, I resort to a series of tables. I start with Table 2 because it contains a comprehensive list of causes.

TABLE 2

Children up to puberty	Cytomegalic virus infections
Healing of a fracture	Hyperphosphatasomia (metabolic defect)
Bone metastases	Intestinal strangulation or obstruction
Rickets	Pseudohypoparathyroidism
Paget's disease of bone	Osteogenic sarcoma
Hyperparathyroidism	Infiltrative liver diseases (sarcoid, granulomas, lymphomas, amyloidosis)
Biliary obstruction	Pancreatitis
Metastatic tumor in liver	Kidney tumors (rarely)
Cirrhosis	Ulcerative colitis with pericholangitis
Alcoholic hepatitis	Multiple myeloma
Fatty metamorphosis of liver	Steatorrhea
Congestive heart failure	Infectious mononucleosis
Pulmonary infarct (one to three weeks after embolism)	Postoperative cholestasis
Pregnancy (third trimester)	

Perhaps you want to concentrate on an organ system. You will probably consider bone and liver first. After all, these two organs harbor the most alkaline phosphatase.

Bone

When a patient has a bone disorder, the chances are serum calcium or phosphorus will also be altered. So, if you are considering a lesion of bone, take a look at Table 3.

Liver Disease

When dealing with possible liver disease, consider the level of the alkaline phosphatase elevation. As you can see in Table 4, the level of elevation tends to vary with the disease. If the other tests on the 12-channel graph and Table 4 fail to clarify your patient's problem, you may want to do a BSP (the single best test of liver insufficiency) or a liver biopsy.

Some Practical Matters

Most of us were taught in medical school that a high alkaline phosphatase meant osteoblastic bone lesions or obstructive liver disease until proven other-

TABLE 3
Summary of Chemical Features of Bone Diseases
Serum

Disease	Calcium	Phosphorus	Alkaline phosphatase
Hyperparathyroidism	Increased	Decreased	Normal or increased
Paget's disease	Normal	Normal	Increased
Hypoparathyroidism	Decreased	Increased	Normal
Renal insufficiency	Decreased	Increased	Normal or increased
Osteomalacia	Decreased or normal	Decreased	Increased
Senile osteoporosis	Normal	Normal	Normal
Multiple myeloma	Normal to increased	Normal	Normal
Milk-alkali syndrome	Increased	Normal to increased	Normal
Vitamin D intoxication	Increased	Increased	Normal
Metastatic carcinoma	Normal to increased	Normal	Normal to increased
Sarcoidosis	Increased	Normal to increased	Normal to increased
Hyperventilation (alkalosis)	Normal	Normal	Normal

*Table adapted from Bernstein, D. S. and Thorn, G. W., in Harrison, T. R., et al. (eds.): Principles of Internal Medicine, 5th ed. McGraw-Hill Book Co., New York, 1966.

TABLE 4*
Alkaline Phosphatase Levels in Liver Disease

Disease	Incidence of Elevated Levels	Usual Range	Incidence greater than 420 units
Hepatitis	80 to 100%	90- 265 units	5%
Obstruction due to Tumor	95 to 100%	425- 850 units	80%
Obstruction due to Stone	95 to 100%	170- 425 units	40%
Infectious Mononucleosis	60 to 70%	85- 850 units	20%
Cirrhosis, Portal	30 to 40%	85- 265 units	5%
Cirrhosis, Postnecrotic	40 to 60%	85- 600 units	15%
Cirrhosis, Primary Biliary	100%	265-1700 units	50%
Space, Occupying Carcinoma in Liver	80%	85-1200 units	20%

*Adapted and modified from Zimmerman, H. J. in Clinical Diagnosis by Laboratory Methods, 13th ed., W. B. Saunders Company, Philadelphia.

wise. Yet these generalizations are not necessarily true. In our experience, these two types of disease processes account for less than half of alkaline phosphatase elevations. And at the Cleveland Clinic, investigators have shown that parenchymal liver disease produces alkaline phosphatase levels of the same magnitude as obstructive lesions.[4] Which means, of course, that you can't always differentiate between hepatocellular and obstructive liver disease with an alkaline phosphatase.

Though you can't depend on past clinical aphorisms, you can closely watch the disease processes that elevate alkaline phosphatases. In adolescents and young adults, for instance, we have noted that infectious mononucleosis is a fairly common cause of high alkaline phosphatases. This is not an isolated observation. In a recent paper, one author has recorded an 85-percent incidence of hepatitis in patients with mononucleosis.[5] Often these patients will have a normal bilirubin.[6] A peripheral smear and a serological test for mononucleosis, then, are indicated tests in a young adult and an unexplained alkaline phosphatase elevation. In older patients, a modest alkaline phosphatase rise,

with or without other abnormal liver function tests, may signal the presence of occult or unconfessed alcoholism. We are currently screening a series of patients admitted to an alcoholic treatment center. So far, 68 of 214 known alcoholics, or 32 percent, have had high values. In the elderly, congestive heart failure commonly produces a slight to moderate rise in alkaline phosphatase. Often this is associated with a BUN rise. If the alkaline phosphatase is high and likewise the LDH, metastatic tumor in the liver looms large as a diagnostic possibility. If the alkaline phosphatase rise is isolated, either Paget's disease of bone or a recent fracture ought to be considered. And so it goes. We hope this letter will help when you are confronted with a high alkaline phosphatase.

Richard L. Reece, M.D.
Minneapolis, Minnesota

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"Mine Spirits"

Paracelsus included in his many medical interests a firsthand investigation of miners' and smelters' ills. He warned against the "mine spirits" of metallic smoke which attack brain, lungs and stomach and recommended preventive monthly doses of essence of tartar; for patients already asthmatic he prescribed cyclamen root liquor. If putrefaction had set in he advised balsam. The patient was further instructed to replace the salt and spices in his food with saltpeter and alum from the mine, prepared like ordinary salt. For miners with jaundice, dropsy, hernia, buboes, ascites, or tympanitis, he prescribed equal parts of wolf's milk and currant juice, or extract of rhubarb with liquor tartari, every morning until the sickness disappeared.*

*The Patient's Progress, Edited by Felix Marti-Ibanez, 1962.

Editor's Note: Paracelsus apparently did not make much of any differential diagnosis. I would be inclined to speculate that he was dealing with carbon monoxide poisoning and that he threw into the category of "Mine Spirits" all the other diseases that miners might suffer whether occupationally related or not. Wolf's milk and currant juice might not be too bad!

Ambition

It is most important in this world to be pushing, but it is fatal to seem so.—Benjamin Jowett

Committee

Medical Service Committee

The principal functions of this Committee are rather broad in nature and involve the investigating and the advising on all aspects of medical service including the socioeconomics of medical practice (30 members). General practice and most major specialties are represented.

Examples of Some Matters Under Consideration

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Of Death and How It Findeth a Man*

How many means and ways has death to surprise us! Who would ever have imagined that a Duke of Brittany should have become stifled to death in a throng of people? Hast thou not seen one of our late kings slain in the midst of his sports? and one of his ancestors die miserably by the throw of a hog? Aeschylus, forethreatened by the fall of a house, when he was most on his guard was struck dead by the fall of a tortoise-shell from the talons of a flying eagle. Another was choked by a grape-pip. An emperor died from the scratch of a comb; Aemilius Lepidus from hitting his foot against a door-sill; Aufidius from stumbling against the door as he was entering the council chamber; Caius Julius, a physician, while anointing a patient's eyes had his own closed by death. And if among these examples I may add one of a brother of mine, Captain St. Martin, playing at tennis, received a blow with a ball a little above the right ear and, without any appearance of bruise or hurt, never sitting or resting, died within six hours afterward of an apoplexy. These so frequent and ordinary examples being ever before our eyes, why should it not continually seem to us that death is ever at hand ready to take us by the throat?

It is uncertain where death looks for us; let us look for her everywhere.

*Montaigne (1533-1592)

Honorable Mention

The June issue* carried the announcement of the MINNESOTA MEDICINE Medical Writing Honor Award winners for 1969.

Now the Board of Editors proudly lists in this issue the authors who received honorable mention for their presentations:

Name	*Manuscript*	*Issue*
John W. Anderson, M.D. *Blue Earth*	*Coronary Care in the Very Small Hospital*	*November*
Aydin M. Bilgutay, M.D. *Nathan Kenneth Jensen, M.D.,* *W. Robert Schmidt, M.D.* *Joseph J. Garamella, M.D.,* *Michael F. Lynch, M.D.* *William D. Kelly, M.D.,* *Minneapolis*	*Mediastinoscopy*	*April*
Roger E. Cupps, M.D. *Malcolm B. Dockerty, M.D.* *Martin A. Adson, M.D.* *Rochester*	*Primary Malignant Lymphoma of Small Intestine*	*December*
Guilford M. Dudley III, M.D. *Newport, Arkansas* *Charles A. Coltman, Jr., Lt. Col.* *USAF, Lackland Air Force Base, Texas*	*Radioisotope Dilution Assay for Vitamin B_{12}*	*March*
John Duffy, M.D. *Joanne L. Hansen, ACSW,* *Minneapolis*	*Psychiatric Aspects of Chronic Lung Disease*	*September*
Dale R. Dunnihoo, Lt. Col., *USAF, Lackland Air Force Base, Texas*	*The Management of Rh ISO-Immunization*	*March*
Robert A. Ersek, M.D. *Shelley Chou, M.D., Ph.D.,* *R. Joel Tierney, B.S.L., LL.B., J.D.* *John S. Najarian, M.D.,* *Richard C. Lillehei, M.D., Ph.D.* *Minneapolis* *Ernest Cutting, B.A., J.D.,* *St. Paul*	*Procurement of Transplantable Tissues*	*January*
Sewell S. Gordon, M.D. *St. Louis Park*	*Regional Enteritis, Early Diagnosis*	*December*
Ramon B. Gustilo, M.D. *Don P. Amren, M.D.,* *Minneapolis*	*Acute Suppurative Arthritis in Children*	*February*
Richard Hong, M.D., *Minneapolis*	*Office Diagnosis of Immunologic Deficiency*	*September*
William B. Kannel, M.D. *Patricia M. McNamara* *Framingham, Mass.*	*The Evidence for Excess Risk in Coronary Disease*	*August*
Myung-Hi Kim Oh, M.D. *John M. Matsen, M.D.,* *Arnold A. Leonard, M.D.* *Paul G. Quie, M.D.,* *Minneapolis*	*Antibiotic Therapy and Hospital-Acquired Infections*	*July*
Russell V. Lucas, Jr., M.D. *Minneapolis*	*Congenital Cardiac Disease*	*September*
P. Lundsgaard-Hansen, M.D. *C. Meyer, M.D.,* *H. Riedwyl, M.D.* *G. Zierott, M.D.,* *Berne, Switzerland*	*Cardiac Metabolism in Experimental Hemorrhagic Shock*	*January*

HONORABLE MENTION

Name	*Manuscript*	*Issue*
Giles F. MacDonald, M.D.	*Prolonged Oxygen Therapy and Mechanical Ventilation*	*November*
David E. Dines, M.D., Alan D. Sessler, M.D. Jack L. Titus, M.D., Rochester		
Carl P. Malmquist, M.D. Minneapolis	*Suicide and Related Clinical Problems*	*October*
Y. Maruyama, M.D. Minneapolis	*Hodgkin's Disease, Current Views on Management*	*April*
John N. Mork, M.D. Worthington	*Hematologic Toxicity of Chloramphenicol*	*October*
Wayne H. Thalhuber, M.D. William R. Swaim, M.D. Minneapolis		
Paul W. Myers, Col. USAF, Lackland AFB, Texas	*Anterior Spinal Fusion*	*March*
Harold O. Peterson, M.D. Minneapolis	*Myelography, Past and Present (1935-1960)*	*December*
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H. Spiess, M.D. M. Mumenthaler, M.D., Berne, Switzerland	*Central European Encephalitis ("Tick-borne Encephalitis") in Switzerland*	*January*
Hans Stirnemann, M.D., Berne, Switzerland	*Treatment of Tetanus*	*January*
Lorenzo F. Trajano, M.D. David A. Berman, M.D., Benjie Goldfarb, M.D., Mary B. Stark, B.D., R.N. Reuben Berman, M.D., Minneapolis	*Treatment of Myocardial Infarction in a Coronary Care Unit*	*May*
William W. Waring, M.D., Judith A. Harris, M.D. New Orleans, Louisiana	*Chronic Lung Disease*	*September*

The Editors again wish to express their thanks and applause to all of the above distinguished authors.

School of Salernum

Now if perhaps some have desire to know,
The number of our bones, our teeth, our veines,
This verse ensuing plainly doth it show,
To him that doth observe, it taketh paines:
The teeth thrise ten, and two, twise eight arow.
Elev'nscore bones save one in us remaines:
For veines, that all may vaine in us appeare,
A veine we have for each day in the yeare:
All these are like in number and connexion.
The difference growes in bigness and complexion.*

*Regimen Sanitatis Salerni

Editor's note: The School here asserts that we humans are all anatomically alike, with 32 teeth, 219 bones, and 365 veins to keep us proud. We differ only in size and color.

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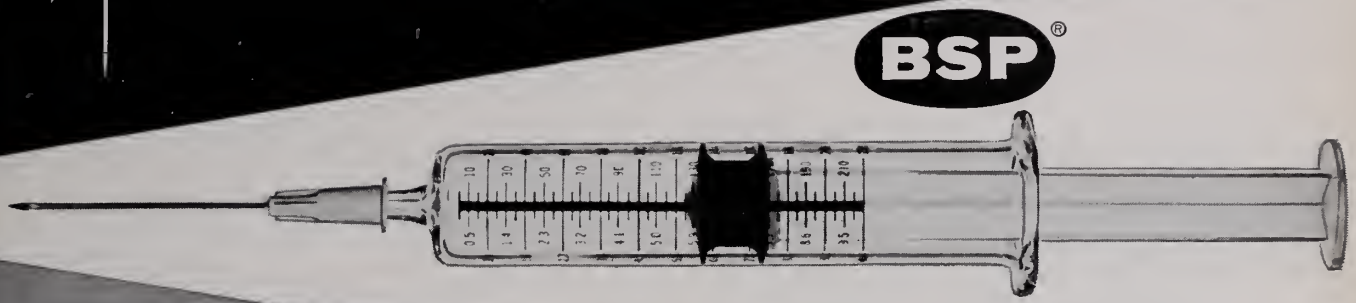
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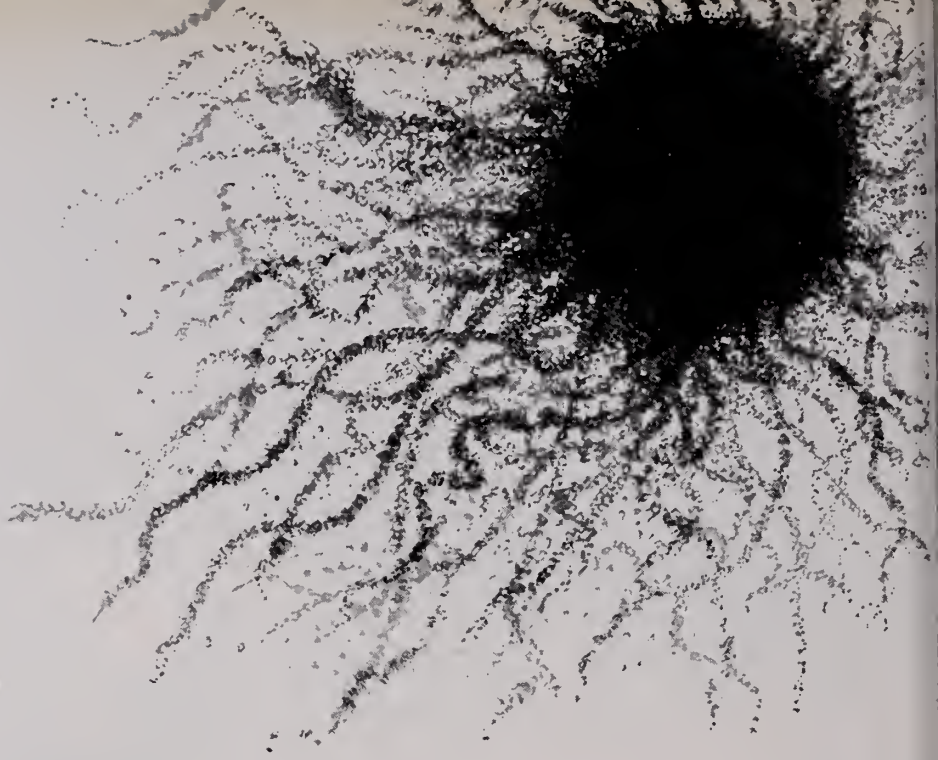
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President's Letter

Britain's National Health Service A 22-Year Experiment?

When the national health service was introduced in Britain in 1948, it was hailed as a social advance which would bring medical care to those who could least afford it. Now, after more than 20 years of trial and error, it has become evident that elimination of the financial barriers between providers and consumers has not removed all problems and in fact has created many new ones.

On a visit to England in 1959 I talked with many physicians, nurses and hospital administrators. Their attitude in regard to the National Health Service at that time varied from mild enthusiasm to "let's give it a chance," even though the program had been in operation for more than 12 years. I also talked with many clients of the Service—cab drivers, hotel clerks, barbers and others. The majority of them were extremely enthusiastic about the plan.

About 10 years later, in 1969 and early in 1970, I was in England twice and talked with some of the persons in the same occupations. There was a remarkable change of attitude; surprisingly, I found that it was not only the providers within the program but principally the ordinary workers, the man on the street and similar citizens who now regard the system as intolerable. One hotel clerk said, "I pay for medical care through burdensome taxes and my family wait in line for hours to get to the doctor and are not infrequently told to return the next day."

To make matters worse, more and more physicians are leaving England because they, in turn, cannot tolerate the assembly-line ordeal of seeing 100 or more patients a day. Consequently, the quality of care has diminished unmistakably. One of my physician friends said that he found himself, out of desperation, in the inexorable position of writing more and more prescriptions for tranquilizing agents without having adequately examined the patients in question. In 1969 he, with some 500 other English practitioners, quit their practice and came to the United States, and many others went to other countries.

In Britain each general practitioner has a base pay of $2,760 per year, plus $2.58 a year for each patient on his list. He gets another $0.33 a year for each patient in excess of the number of 1,000, plus $2.40 for a night call, $0.60 to $0.90 for various inoculations and $38.10 for a maternity attendance. He can earn up to $3,400 a year more for such things as practicing in a group clinic, for seniority in service, or for transferring to an area in which there is a shortage of physicians. All these payments can bring the average physician's income to about $11,500 a year. Nurses

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Folic Acid Deficiency

Multiple Complications

A. DOSCHERHOLMEN, M.D., Ph.D.*

Folic acid and vitamin B_{12} deficiencies are the most common causes of megaloblastic anemia.[1] Although a reliable method for serum vitamin B_{12} determination has been available since 1952,[2] it was not until 1960 and 1961 that dependable methods for serum folate assay[3,4] became available. The clinical experience at the Veterans Administration Hospital, Minneapolis, with the measurement of the serum folate activity for a two-year period beginning February 1964 is related here.

Materials and Methods

Serum folate bioassay was performed with *Lactobacillus* casei, according to the method of Waters and Mollin.[4] With this assay, normal values in Great Britain ranged from 5.9 to 21.0 nanograms per milliliter (ng/ml).[4] In the United States, Herbert and associates found normal values from 7.5 to 24 ng/ml.[3] From a study of alcoholic patients, Herbert and coworkers concluded that values below 3.0 ng/ml were indicative of folic acid deficiency, values of 3.0 to 4.9 strongly suggestive of folate deficiency, and values from 5.0 to 6.9 in the indeterminate range.[5,5a] Normal values in 10 subjects in this study ranged from 7.0 to 16.0 ng/ml.

*Medical Service, Veterans Administration Hospital and the University of Minnesota Medical School, Minneapolis, Minnesota.

The Controls

Various authors have found somewhat differing normal values for serum folate activity;[6] each laboratory should therefore establish its own normal range for this test. In 24 healthy laboratory technologists selected as our controls, values ranged from 6.4 to 25.6 ng/ml. Serum from each control was assayed at one-to-three-week intervals. The average values were 11.7, 11.9 and 12.1 ng/ml, respectively. The reproducibility of within ± 10 percent in 15 cases, 10 to 15 percent in seven, and 15 to 20 percent in two was very satisfactory. In our laboratory, therefore, values below 6.4 ng/ml are considered subnormal.

Serum vitamin B_{12} was determined using the Euglena gracilis method.[2] In the 24 controls, values ranged from 260 to 788 picograms per milliliter (pg/ml). Vitamin B_{12} absorption was measured using the plasma absorption method.[7] Control values for this test range from 1.9 to 11.4 pg/ml, with an average of 4.8 when an oral test dose of 0.56 μg radiocyanocobalamin is given.[8]

The methods of Ramsay[9,10] were used to determine the serum iron and the total iron-binding capacity.

At the time of the folate assay, two quantitative measurements for hypersegmentation of the nuclei of blood neutrophils were applied:[11,12] (a) the percentage of neutrophils with five or more nuclear lobes and (b) the average lobe count. The nuclear lobes of 200 neutrophils were counted and the cells with various numbers of lobes were totaled. In the control group, the highest percentage of cells with five or more lobes was 3.5 (range 0 to 3.5). By this criterion, any figure above 3.5 indicates hyper-

TABLE 1
Serum Folate Values in 261 Patients

Study Group	Number of Patients	Serum Folate Values (ng/ml)		Age of Patients (years)		Time from Admission to Folate Assay (days)	
		Range	Average	Range	Average	Range	Average
I. Indicative of Folate Deficiency	61	0.0-3.0	2.3	34-88	60.0	0-262	26.7
II Strongly suggestive of Folate Deficiency	114	3.1-5.0	4.2	31-90	61.0	0-199	17.0
III Diagnostically indeterminate	86	5.1-6.4	5.6	32-92	60.7	0-151	15.7
I-III	261	0.0-6.4	4.2	31-92	60.7		

segmentation. The average lobe count was obtained by dividing the total number of lobes in 200 neutrophils by the number of cells. In the 24 controls, the highest average lobe count was 3.2 (range 2.4 to 3.2). By this criterion, any figure above 3.2 indicates hypersegmentation. Standard techniques were used in all other laboratory tests.

The subjects in our series were hospital patients who had hypersegmentation of neutrophils or whose physician requested a serum folate assay in the routine investigation of anemia.

The Clinical Material

Subnormal serum folate levels were found in 261 patients, one of whom was female (Table 1). The patients were divided into three groups according to folate values: Group I, values up to 3.0 ng/ml; Group II, values of 3.1 to 5.0 ng/ml; and Group III, values of 5.1 to 6.4 ng/ml, our lowest normal value.

The majority of patients had multiple diagnoses (Table 2). The most common illnesses were infections, alcoholism and Laennec's cirrhosis, cancer and blood dyscrasias, and pulmonary, gastrointestinal, genitourinary, neurologic, endocrinous and metabolic diseases.

TABLE 2

Diagnosis in 261 Patients with Folic Acid Deficiency*

Diagnoses	Number of Patients
1. Alcoholism	82
2. Laennec's cirrhosis of the liver	40
3. Cancer	59
4. Blood dyscrasias	12
5. Gastrointestinal diseases	85
6. Infections	118
7. Cardiovascular diseases	64
8. Pulmonary diseases	41
9. Genitourinary tract diseases	51
10. Endocrinous and metabolic diseases	36
11. Skin diseases	9
12. Diseases of the nervous system	45
13. Mental illnesses	17
14. Malnutrition	13
15. Thromboembolism	15
16. Fractures and joint injuries	17
17. Rheumatoid arthritis	10
18. Pernicious anemia	3
19. Miscellaneous	50

*The majority of patients had multiple diagnoses

Results

Incidence of Anemia

Hemoglobin determination revealed that 89.5 percent of the patients had values below 14 gm per 100 ml of whole blood, indicating anemia of various degrees in the three groups.

The type of anemia is best characterized by the Wintrobe[13] indices. Of the normal population about 93 percent fall within the normal range of these indices. The mean corpuscular volume was obtained in 158 patients, 98 (62 percent) of whom had macrocytosis (MCV $>$ 92 μ^3) and five (3.2 percent) microcytosis (MCV $<$ 82 μ^3). The average mean corpuscular volume was increased in all three groups, with the highest value in Group I (100.4 μ^3) and the lowest in Group III (95.2 μ^3) without statistical significance ($p > 0.5$).

The mean corpuscular hemoglobin concentration values were obtained in 161 patients, in 76 of whom (47.2 percent) the mean corpuscular hemoglobin concentration was decreased to less than 32 percent, indicating hypochromic anemia. The average figure was below the normal value of 34 percent in each of the three groups.

White Blood Cells and Platelets

Leukopenia or thrombocytopenia, or both, may occur in folic acid deficient and megaloblastic anemias. In our series, leukopenia was seen initially in 25 patients and thrombocytopenia in 18 patients. In 10 patients the white blood cell and platelet counts were abnormally low. The white blood cell count returned to normal in 13 patients and the platelet quantity became normal or improved significantly during hospitalization. Failure of the white blood cell count or the platelet quantity to improve or become normal was ascribed to the underlying disease or myelosuppressive therapy.

Hypersegmentation of Blood Neutrophils

Blood films were obtained in 229 patients at the time of the folate assay. The quantitative lobe count showed hypersegmentation in 90.8 percent of these patients, as determined by an increased percentage of neutrophils with five or more lobes. Though the average lobe count was increased in 72.9 percent, it was the least sensitive. No significant difference was apparent in the percentage of hypersegmentation in the three groups.

Bone Marrow Examinations

Bone marrow biopsies were performed in 55 patients, 18 of whom showed megaloblastosis. In Group I, megaloblastosis was twice as common as in Group II and three times as common as in Group III. The average time between admission and bone marrow examination was 16 to 18 days for patients who had megaloblastosis as compared with 32 to 37 days for those with normoblastosis.

Marrow iron was decreased or absent in 17 patients (30.9 percent), increased in 26 (47.3 percent), and normal in 12 (21.8 percent).

Serum Vitamin B_{12} Concentration and Vitamin B_{12} Absorption

Serum vitamin B_{12} concentrations were obtained in 249 patients. Eight had absolute B_{12} deficiency, with values below 100 pg/ml; 14 had relative deficiency, with values of 100 to 150 pg/ml. The values fell in the low borderline range of 150 to 250 pg/ml in 32 patients and were above the commonly quoted upper normal range of 900 pg/ml[14] in 36. The remaining 159 patients had values within the normal range.

Three of the eight patients with absolute deficiency had pernicious anemia; the remaining patients had undergone Billroth II gastric resection nine to 19 years previously. Of the 14 patients with relative deficiency, three had alcoholism or cirrhosis of the liver, three had cancer, two had undergone gastric surgery, two had severe infection, and one each had chronic brain syndrome, schizophrenia, multiple myeloma and benign prostatic hypertrophy.

Of the 36 patients with increased serum vitamin B_{12} concentrations, 13 had Laennec's cirrhosis, two had alcoholism, four had uremia with heart failure, five had cancer with metastases, three had chronic myeloid leukemia, four were on vitamin B_{12} therapy, three had arteriosclerosis with heart failure, one had benign gastric ulcer, and one had pulmonary emphysema.

Vitamin B_{12} absorption studies were done in 69 patients, 24 of whom had abnormally low absorption values. One National Formulary unit of hog intrinsic factor concentrate* was given to the patients with abnormal B_{12} absorption, but failed to correct the absorption values in five patients. The average absorption value without intrinsic factor was 1.1 pg/ml and with intrinsic factor 3.8 pg/ml. Absorption values returned spontaneously to normal in three of four patients who were restudied after four to eight weeks. In patients with vitamin B_{12} levels below 100 pg/ml the average absorption value was 0.8 pg/ml. The corresponding values in patients with serum levels of 100 to 150 and 150 to 250 pg/ml were 2.9 and 4.8 pg/ml, respectively. These findings show a good correlation between the absorption of radiocyanocobalamin and the level of serum vitamin B_{12}.

Serum Iron and Total Iron-Binding Capacity

Of the 147 patients who had serum iron determinations, 62.6 percent had abnormally low values (below 55 μg percent), 35.4 percent normal values (55 to 175 μg percent), and 2 percent increased values (above 175 μg percent). The average values of 61, 58 and 49 μg percent in the three folate deficiency groups are far below the average normal value.

Because many of these patients had chronic infection, inflammation, cancer or uremia, all of which may be associated with hyposiderinemia, the total iron-binding capacity, as well as serum iron values, was needed for accurate evaluation of the iron metabolism. Of the 140 tested, the total iron-binding capacity was decreased in 31.4 percent, increased in 2.9 percent, and normal in the rest.

The percentage of transferrin saturation is a fairly reliable index of the body iron stores.[15] Of 140 patients tested, the transferrin saturation level was below 15 percent (absolute iron deficiency) in 57 patients (40.7 percent), and between 15 and 25 percent (relative iron deficiency) in 40 patients (28.6 percent). Eleven patients had increased saturation levels; only 32 had normal levels (25 to 50 percent). Since the iron determinations in patients with hypochromasia were only slightly higher than those with normochromasia (78.9 and 69.4 percent, respectively), the figures related to iron metabolism seem fairly representative for the entire study group.

Gastric Analysis

Gastric analysis was done in 112 patients, in whom the average age was 61.9 years. Histamine-fast achlorhydria was present in 35.7 percent of these patients, which is about as expected for this age group.[16]

Response to Treatment

Folic Acid Therapy

In the 98 patients who received folic acid therapy 5 to 15 mg daily and had both initial and final hemoglobin determinations, the aver-

*Commercially obtained from Abbott Laboratories, Chicago, Illinois.

age hemoglobin value rose from 10.0 to 11.5 gm percent, an increase of 15 percent, with seven patients (7.1 percent) attaining a normal hemoglobin. In the 113 patients who received diet only, the average hemoglobin rose from 10.9 to 11.3 gm percent, an increase of 3.7 percent with nine patients (8 percent) attaining a normal hemoglobin value. Although the average hemoglobin value was increased more with folic acid than with the hospital diet, the percentage of patients attaining normal values did not increase significantly. Chloramphenicol, a bone marrow depressant, had been administered to 65 patients, in whom the average hemoglobin decreased from 12.0 to 11.6 gm percent. If the values of these patients had been excluded from the data, the response to treatment would have been slightly higher.

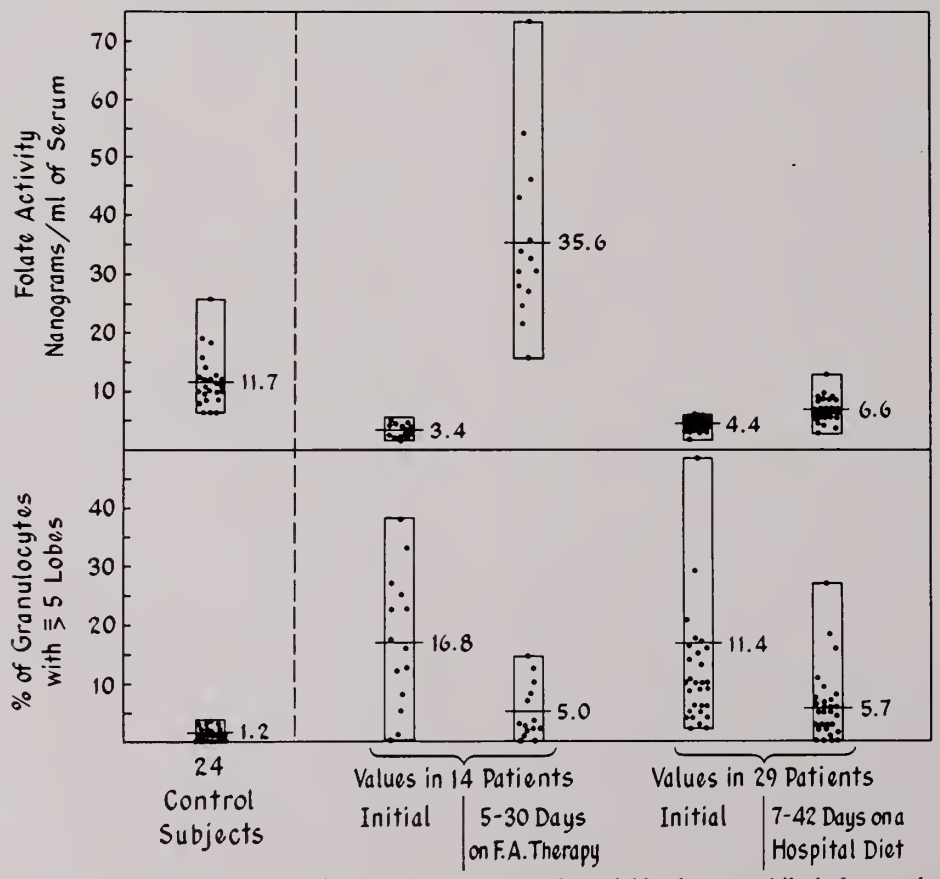
Iron Medication

Iron medication was given to 63 of the 97 patients with known low or borderline saturation of transferrin. In response to therapy the average hemoglobin value rose from 9.6 to 11.3 gm percent, an increase of 17.7 percent, with four patients attaining a normal level. In the 34 patients who did not receive iron therapy, the average hemoglobin rose from 10.7 to 11.4 gm percent, an increase of 6.5 percent, with only one patient attaining a normal level.

Vitamin B_{12} Administration

Vitamin B_{12} was administered to the eight patients with absolute vitamin B_{12} deficiency. Their average hemoglobin value increased from 11.2 to 11.9 gm percent. Two of these patients attained normal hemoglobin level, six did not. Of these six patients, two had terminal cancer and two had persistent gastrointestinal bleeding, associated with Rendu-Osler-Weber's disease and Henoch-Schoenlein purpura. The remaining two patients were lost to inadequate follow-up.

We did follow-up on serum folate levels and hypersegmentation in 14 patients treated with 5 to 15 mg of folic acid daily and 29 patients given a hospital diet with no additional folic acid therapy (Figure). The average



Figure—Serum folate activity and hypersegmentation of blood neutrophils before and after treatment with folic acid or a hospital diet. The average values for foliate activity were increased and the hypersegmentation was decreased with both types of treatment. However, the response was greater with folic acid therapy.

interval between the first and the second assay was 14.6 and 19.6 days in the two groups, respectively. The average serum folate value rose 1000 percent in the former group and 50 percent in the latter. The average value for hypersegmentation declined by 70.2 percent in the former group and by 50 percent in the latter. In four of the patients treated with diet only, a second folate assay made 14 to 42 days (average 30 days) after the first showed a drop in the average folate value from 5.0 to 3.9 ng/ml. Although the serum folate levels did not respond to diet in these four patients, hypersegmentation disappeared in two of them, improved in one, and was unchanged in one. The two patients in whom hypersegmentation disappeared probably used the food folate as rapidly as it was absorbed. The patient in whom hypersegmentation did not improve had acute cholecystitis and tuberculosis, for which he was receiving continuous isoniazid therapy. Low serum folate levels are not uncommon in tuberculous patients,[17,18,19] although the reason for this is not entirely clear.[17]

Discussion

Frequency of Folic Acid Deficiency

The finding of folate deficiency in 261 patients within a two-year period suggests that the deficiency occurs more frequently than is generally realized. Moreover, this figure must be regarded as minimum for two reasons. First, latent or preclinical deficiency was not particularly sought for except in special patients for whom the resident physicians requested folic acid determinations. Second, serum folate levels may be normal in some patients with hematologic and clinical evidence of folate deficiency.[20-22] Many patients with folate deficiency may have multiple diagnoses. Our study showed a high incidence of chronic debilitating illnesses, reflected by the 19.9 percent fatality rate during the hospital stay in which low folate levels were obtained.

Serum Versus Red Blood Cell Folate Determination

Serum folate determination is a satisfactory and sensitive test when used with serum vitamin B_{12} assay to investigate megaloblastic anemias.[3,4,5,23] Red blood cell folate concentrations may be of special value in patients with borderline serum folate levels,[23] though they cannot be used to differentiate primary folate deficiency from pernicious anemia, since patients with vitamin B_{12} deficiency often have low red blood cell folate levels.[23] For accurate diagnosis, therefore, red blood cell folate concentration tests should be done in conjunction with those for serum folate and vitamin B_{12}.

Pathogenesis

In our patients, no special studies were performed to elucidate the pathogenetic mechanism. In many patients, folate deficiency was due to several factors, such as increased utilization of the vitamin by a rapidly growing tumor,[24] a malignant hematologic disease,[25] or a hemolytic anemia[26-28] together with a poor diet. In some patients, gastrointestinal disease[29-31] or gastrointestinal surgery[32] increased the possibility of malabsorption; and in alcoholics, the small amount of food folate ingested may have been poorly assimilated.[33] Because of the causal complexity of folate deficiency in many cases. the diagnoses rather than the causes were given.

Absorption of Folic Acid

Folic acid is generally believed to be absorbed from the upper part of the small bowel,[34] whereas vitamin B_{12} is absorbed from the ileum.[35] Apparently there is an active energy-requiring mechanism of absorption for physiologic amounts of these vitamins and a passive mechanism for supraphysiologic quantities, depending on the concentration gradient.[36] Although the active mechanism appears site-specific, the passive mechanism may operate throughout the length of the small bowel.

In sprue syndromes, folate deficiency may develop despite a normal intake of the vitamin.[37] The disease may respond to synthetic folic acid given orally in doses that are less than 5 percent of the total dietary intake of folates, indicating poor assimilation of food folates.[37] In some cases of sprue, the conjugase activity is low in the intestinal juice[38] and normal in the plasma.[39] The conjugase activity in the intestinal epithelial cells is probably the more important. Although this enzyme has been identified in the intestinal mucosal cells in normal subjects, its activity in sprue is unknown.[40]

Daily Requirement

The daily requirement for folic acid has been estimated from the results of both experiments on normal subjects receiving a low-folate diet

and treatment of patients with folate deficiency receiving titrated doses of folic acid. In man, the normal daily requirement for folic acid is about 50 to 100 μg.[41-43] In some cases of sprue with folate deficiency, good response to daily oral therapy of 5 to 25 μg of synthetic folic acid has been reported;[37,44] in other instances of folate deficiency, definite response has required as much as 200 μg.[45] In disease states, the minimum daily requirement for this vitamin seems to vary with the patient's need. Some hemolytic states with megaloblastic anemia may require as much as 500 to 1000 μg daily for definite response,[27,28] whereas in special physiologic states, such as in pregnancy, the daily requirement may be as high as 300 μg.[46]

Body Stores

The normal body stores of folates in man range from 5 to 10 mg.[47] The liver, believed to be the most important storage organ for folates, contains an average of 5 μg per gram of tissue in the form of 5-methyl-tetrahydrofolic acid.[48] It is believed that most folate circulating in the blood is in this form,[49] although recently 5-methyldihydrofolate also has been demonstrated in the blood.[50] A healthy young man was given a diet very low in folates. Four and one-half months passed before his body stores were exhausted to the extent that megaloblastic anemia ensued.[41] The development of acute folic acid deficiency when folate intake or absorption ceases[51] is explained on the basis of initially low body stores of folates.[12] In experimental folic acid deficiency, subclinical or biochemical deficiency is present for several weeks before any hematologic changes occur.[41]

Morphology

Folic acid in the organism is converted to various coenzyme forms that function in single carbon transfer reactions.[47] It is reduced to tetrahydrofolic acid, the coenzyme form that acts as an acceptor for various one-carbon units. The metabolic processes involving folate coenzymes are (1) de-novo synthesis of purines, (2) synthesis of pyrimidine nucleotides, (3) various interconversions of amino acid (serine to glycine, homocysteine to methionine, and catabolism of histidine to glutamic acid), and (4) generation and utilization of formate.[47] Thus folic acid has a very important role in nucleoprotein metabolism. The metabolic interrelations and the significance of the recently discovered 5-methyldihydrofolate[50] await further clarification.

Blood and Bone Marrow Picture in Folate Deficiency

The morphologic picture of the blood and bone marrow in folate deficiency is identical to that in vitamin B_{12} deficiency.

In 10.5 percent of our patients, the hemoglobin was normal, probably due to the short duration of the folate deficiency. Anemia was present in 89.5 percent of the patients. Megaloblastic anemia in folate deficiency[52] may differ from that in pernicious anemia, because vitamin B_{12} therapy usually results in complete remission of the latter.[53]

A macrocytic anemia was present in 62 percent of the patients. The average reticulocyte count was only slightly elevated (2.5 percent). Vitamin B_{12} deficiency may have contributed to the macrocytosis in the eight patients in whom this deficiency was absolute and possibly in the 14 patients in whom it was relative. However, folate deficiency was probably the major contributing factor, since the macrocytosis was most pronounced in the group with the lowest average folate level and least pronounced in the group with the highest average level.

Leukopenia and thrombocytopenia are not uncommon in megaloblastic anemia and were present in some of our patients. Failure of these disorders to respond to folic acid therapy or a good hospital diet could usually be attributed to underlying illnesses or to myelosuppressive drugs.

Hypersegmentation of blood neutrophils is an early and very sensitive index of folic acid deficiency and/or megaloblastic bone marrow.[11,12,41] Hypersegmentation was found in 90.8 percent of our patients. In the 9.2 percent of the patients with no hypersegmentation, the folate deficiency was probably of too short duration to influence the granulocyte maturation; these patients had latent or preclinical folate deficiency.[41]

There was no significant difference in the incidence of hypersegmentation in the three groups of folic acid deficiency. If the time intervals between hospital admission and lobe count had been the same in the three groups, that is, 10 to 11 days longer in Groups II and III, these two groups might have shown less hypersegmentation. This contention is supported by the results obtained from the second folate assays in the group who received only the hospital diet.

The value of dividing the material into three groups is more evident in the bone marrow findings which showed an increased tendency to megaloblastosis as serum folate levels decreased. The average time interval from admission to bone marrow testing was about the same in the

three groups.

Vitamin B_{12} Metabolism

In our series serum vitamin B_{12} values ranged from abnormally low in eight patients to abnormally high in 36; in 63.8 percent of patients the serum vitamin B_{12} levels were definitely normal. Mollin and coworkers[20] were the first to report increased serum folate levels in pernicious anemia in relapse. Later reports have shown that in this phase of the disease the serum folate concentration may be increased, normal or decreased.[54,55] Our eight subjects with absolute vitamin B_{12} deficiency had decreased folate levels and low vitamin B_{12} absorption values corrected by the addition of intrinsic factor.

In primary folate deficiency, it is not unusual to observe low serum B_{12} levels[56] and vitamin B_{12} absorption values.[57] Folic acid therapy may correct both of these abnormalities.[57,58] The borderline or low normal serum B_{12} values in our patients probably can be explained on this basis, since the vitamin B_{12} absorption values returned to normal in four to eight weeks in three of four patients tested.

The supranormal serum vitamin B_{12} levels were presumed to be the sequel to vitamin B_{12} therapy in four cases, chronic granulocytic leukemia in three,[59] and liver disease in 27 (alcoholic liver disease in 15,[60] cancer with liver metastases in five,[61] and arteriosclerotic heart disease and uremia with heart failure and passive congestion[62] of the liver in seven). The high serum B_{12} concentration in one patient with benign gastric ulcer and in one with pulmonary emphysema is more difficult to explain. Perhaps their individual values, 1085 and 945 pg/ml, respectively, are within the uppermost normal range.[14]

Iron Metabolism and Folic Acid Deficiency

Hypochromic anemia as judged by the low mean corpuscular hemoglobin concentration was present in 47.2 percent of the patients, and a total of 28.5 percent showed a dimorphic blood picture, with mean corpuscular volume above 92 μ^3 and a mean corpuscular hemoglobin concentration below 32 percent. Hypochromic anemia is usually due to iron deficiency and rarely to inability to utilize iron. Of 13 patients with mean corpuscular hemoglobin concentration below 32 percent and normal or increased transferrin saturation, the hypochromic anemia may have been caused by other factors.

Transferrin saturation iron deficiency[15] was absolute in 40.7 percent and relative in 28.6 percent of our patients. It has been observed that in response to therapy for megaloblastic anemia, transferrin saturation may drop below normal levels in the absence of a total body iron deficit.[63] Perhaps some of our patients were responding to the dietary folate at the time the transferrin saturation was determined. Thus bone marrow iron content may be a better means of determining body iron storage.[15]

In 17 of 55 of our patients, bone marrow iron was decreased or absent; in 12 it was normal. Three of the 12 patients had megaloblastic anemia, with an average hemoglobin of 9.8 gm percent.

Considering the measurements of the mean corpuscular hemoglobin concentration, transferrin saturation, and bone marrow iron content, it is difficult to state the exact percentage of iron deficiency in our series of patients, but a reasonable estimate is about 40 percent. Clinical observations[22,64,65] and experimental animal studies[66] indicate a relationship between primary iron deficiency and folate deficiency.

Multiple Deficiencies

Low values for folic acid, vitamin B_{12} and transferrin saturation coexisted in a number of patients. Table 3 shows that the percentage figure of multiple deficiencies in 140 patients in whom this data were available ranged from 0.7 to 15.0, depending on the criteria for the lower normal values. Multiple deficiencies of these three hematinic substances are common in patients with gastrointestinal diseases such as sprue or malabsorption or who have had gastrointestinal operations.[11,40,67]

TABLE 3

Multiple Deficiencies of Iron, Vitamin B_{12} and Folic Acid in 140 Patients

Deficiencies			Patients	
Transferrin Saturation (percent)	Vitamin B_{12} (pg/ml)	Folic Acid (ng/ml)	Number	Percent
<15	<100	<6.4	1	0.7
<15	<150	<6.4	6	4.3
<15	<260	<6.4	16	11.4
<25	<150	<6.4	9	6.4
<25	<260	<6.4	21	15.0

Conclusions

Our study shows that both folic acid therapy and a good hospital diet can increase the average serum folate concentration and concomitantly reverse the hypersegmentation of the

neutrophils and megaloblastosis. Though folic acid therapy accomplished this result in a shorter period of time, the average hemoglobin level became only slightly elevated. A beneficial effect of folic acid therapy was definitely demonstrated, however, by the average hemoglobin value being greater in patients receiving folic acid therapy than in patients receiving only a hospital diet.

Failure of hemoglobin to reach normal levels on therapy with folic acid, iron and vitamin B_{12} usually could be ascribed to underlying chronic illnesses or, in some instances, to treatment with myelosuppressive drugs.

Summary

The patients in this series had a wide variety of illnesses, but most of them had chronic debilitating diseases, and multiple diagnoses were common. Approximately 90 percent of the patients were anemic, with macrocytosis in 62 percent and hemoglobin deficiency in 47 percent of those patients in whom red blood cell indices were done. Hypersegmentation of the blood neutrophils, a sensitive index of folic acid deficiency and megaloblastic bone marrow, was observed in about 90 percent of the cases.

Improvement in or reversal of hypersegmentation usually occurred with both hospital diet and folic acid therapy. The latter form of therapy was effective in less average time.

Leukopenia and thrombocytopenia were present in some patients. Failure of the white blood cell and platelet count to respond to treatment could be ascribed to the underlying diseases or to the action of myelosuppressive drugs.

Bone marrow examinations showed a good correlation between low serum folate levels and megaloblastic anemia. Vitamin B_{12} serum levels ranged widely from abnormally low values in 8.8 percent of the patients to abnormally high values in 14.5 percent. Iron deficiency was present in about 40 percent of the patients.

The failure of hemoglobin levels to become normal in patients with iron and B_{12} deficiencies when these hematinics were given was assumed to be related to the underlying chronic diseases and in some instances to myelosuppressive drugs

Low values for folic acid, vitamin B_{12} and transferrin saturation coexisted in some patients, and the percentage figure for multiple deficiencies of these hematinics was given.

Acknowledgment

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Don't mistake pleasure for happiness. They are a different breed of dogs.—Joselyn Dillings.

Hepatorenal Toxicity of Tetracycline

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Reports have defined a rather characteristic syndrome characterized by hypoproteinemia, jaundice, progressive azotemia with high urine output, acidosis, and bleeding tendencies. Histologically the syndrome is characterized by fine, fatty vacuolization of liver cells without evidence of liver cell necrosis or intrahepatic bile stasis. There have been reports of studies in men and animals suggesting hepatic and renal toxicity of the tetracycline drugs dating back to at least 1951.[1,2,3,4] There was some uncertainty as to the clinical significance of these early studies, as the cases involved had other fatal diseases, and other studies either did not indicate serious hepatorenal toxicity or suggested that any such effect was rapidly reversible. With respect to possible renal toxicity, some confusion was caused by the fact that the tetracyclines have a catabolic or antianabolic effect on protein metabolism, causing speculation that the rises in blood urea nitrogen observed in many studies were not due to renal toxicity but to a pre-renal azotemia.[5]

In 1963 Schultz et al. reported six cases of a fatal outcome in young, pregnant women who received high doses of intravenous tetracycline.[6] This report was followed by other reports of hepatorenal toxicity attributed to tetracyclcline in pregnancy.[7,8,9] Subsequently further cases were reported in nonpregnant women[10,11,12] and in a man on estrogen therapy.[13]

This report describes seven patients who manifested clinical and histologic evidence of tetracycline toxicity: three men and four nonpregnant women. Blood specimens were available for tetracycline assay in three patients, and excessively high blood levels were found in each case. These patients are described in detail. On review of our autopsy records, four additional cases were encountered and these are summarized briefly.

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Report of Cases

Case 1

The patient was a 77-year-old white male admitted to the hospital on June 17, 1969. For about four to five months prior to admission he had experienced anorexia and a 20-pound weight loss. Past history indicated a diagnosis of carcinoma of the urinary bladder made and treated in 1956 with no subsequent evidence of recurrence. He was known to have diverticulosis of the urinary bladder and a consequent chronic cystitis due to diverticulitis of these diverticula. A diabetic glucose tolerance test was made in 1966. Physical examination was not remarkable except for some evidence of peripheral arteriosclerosis. Hemoglobin was 12.8 grams; leukocyte and differential counts were normal. A chemistry screening profile which included blood sugar, sodium, potassium, CO_2 combining power, chloride, calcium, protein, BUN, uric acid, bilirubin and glutamic oxalacetic transaminase were all normal except for a BUN of 27 milligrams percent. The repeat BUN was the same. Liver function tests, including glutamic oxalacetic transaminase (SGOT) and glutamic pyruvic transaminase (SGPT), bilirubin, alkaline phosphatase and fractional proteins were normal except for a slight reduction in the albumin to 3.4 grams percent. A cystoscopy revealed only previously noted diverticulosis of the bladder. Urine culture resulted in 150,000 colonies of *E. coli* per cubic centimeter. A retrograde pyelogram was normal.

A colon x-ray was interpreted as showing a constricting lesion in the upper sigmoid colon consistent with carcinoma. Clinical impressions at this point were (1) carcinoma of the sigmoid colon; (2) chronic diverticulitis and cystitis of the urinary bladder; (3) nephrosclerosis with mild renal insufficiency; (4) generalized arteriosclerosis. After a bowel preparation of the patient with 8 grams of sulfasuxadine a day for three days and 7 grams of neomycin per day for two days, the abdomen was explored on June 26, and a tightly constricting carcinoma of the left colon was encountered, which was resected. There was no evidence of spread of the tumor, and the lesion was classified pathologically as a Duke's type B adenocarcinoma of the colon. The patient tolerated the procedure well, and his immediate postoperative course was satisfactory.

Tetracycline Administration

From June 26 to June 29 the patient was given a total of 6 grams of tetracycline intravenously, with doses ranging from 1.5 to 2.5 grams in a 24-hour period. From June 29 to July 1 he received from 0.75 to 1 gram of tetracycline orally for a total of 2.5 grams. Monitoring

of electrolytes showed them to remain within normal limits. The first BUN postoperatively, however, was not done until July 1, at which time it was 78 milligrams percent. On the morning of July 5 he looked rather pale and his blood pressure had fallen to 64 millimeters of mercury systolic. He then began to have melena and his hemoglobin dropped to 7 grams. He was given a total of 12,500 cubic centimeters of blood during the next 36 hours.

On July 6 his upper abdomen was explored and a large, posterior ulcer was found just distal to the pylorus. A Billroth II subtotal gastrectomy was done. He tolerated this procedure satisfactorily, and there was no further evidence of bleeding. He had a good urinary output at all times. His BUN, however, remained elevated. On July 12 it was noted that he was jaundiced. His bilirubin was 3.9 milligrams per cent. SGOT and SGPT were 125 units. Alkaline phosphatase was normal. Serum proteins had decreased to 3.5 grams percent total with 2.2 grams percent albumin and 1.3 grams percent globulin. Tetracycline had been restarted intravenously on July 6 following the second operation and was given in doses of 1 to 3 grams daily intravenously July 6 through July 11 for a total of 12.5 grams. On July 12 he suddenly vomited fresh blood and began to have melena again. Prothrombin times were prolonged. A fibrindex test showed a normal amount of fibrinogen. Bleeding and clotting times were within normal limits; platelet count was 100,000. Therapy consisted of irrigation of the stomach with iced water, fluid and electrolyte management, and whole blood transfusions with fresh frozen plasma. The patient died on July 15, 1969.

Autopsy Findings

Autopsy findings included acute segmental small bowel infarctions. There were also focal areas of mucosal erosion and hemorrhage in the distal esophagus and colon. Histologic sections of liver showed fine fat vacuolization involving the major portion of the lobules, characteristic of tetracycline toxicity. Sections of kidney revealed small numbers of refractile crystalline casts in the tubular lumens and minor, nonspecific, degenerative changes in the tubular epithelium.

An assay of tetracycline was performed on a blood specimen obtained three days before death. A value of 73 micrograms per milliliter was obtained by a microbiologic method and 70 micrograms per milliliter by a chemical method.

Comment

It would seem probable that in this case tetracycline toxicity was instrumental in the patient's death. The patient had mild renal insufficiency prior to his first operation which he negotiated uneventfully. Intravenous tetracycline, however, undoubtedly could not be excreted properly, and toxic levels began to build up with a nephrotoxic effect, causing further renal insufficiency; hence a vicious circle was established. As seen in other cases of renal tetracycline toxicity, this patient was able to excrete large amounts of isothenuric urine with increasing azotemia. Phosphate also began to build up. The toxic effect of tetracycline on the hepatic cells was also manifest by increasing bilirubinemia, decreased protein synthesis, prolonged prothrombin time, and enzyme changes. The prolonged prothrombin time undoubtedly reflected decrease in accessory coagulation factors as well as prothrombin.

Case 2

The patient was an 87-year-old white male admitted to the hospital with a fractured hip which was treated surgically. His BUN on admission was 30 milligrams percent. Two weeks postoperatively the BUN had been 34 milligrams percent. The patient was confused, and his fluid intake was poor. He began to run a low-grade fever, and three days later the BUN had risen to 111 milligrams percent. At this time he was given tetracycline intravenously in doses of 1 gram per day for two days, omitted for two days, and then restarted in doses of 1 to 2 grams per day for seven more days. The total intravenous tetracycline was 13.2 grams. The BUN continued to rise to 135 milligrams percent, and the patient died.

The autopsy revealed a small renal cortical abscess with a large perirenal abscess. The fine fatty vacuolization noted in this case involved primarily the central portions of the liver lobules. Microscopic sections of kidney revealed large numbers of crystalline casts in the renal tubules as well as nonspecific degenerative tubular changes and moderate arteriolar nephrosclerosis.

Tetracycline levels obtained on a post-mortem blood specimen revealed a level of 50 micrograms per milliliter by a microbiologic method and 60 micrograms per milliliter by a chemical method.

Comment

This patient showed characteristic liver and renal pathological findings associated with tetracycline toxicity; although undoubtedly tetracycline toxicity played a relatively minor role in the ultimate outcome.

Case 3

The patient was a 56-year-old white female admitted to the hospital in shock with an *E. coli* septicemia associated with a pelvic abscess. She was treated with Ampicillin in doses of 8 grams daily intravenously, Methicillin 4 grams daily intravenously, and tetracycline 1.5 to 2 grams daily intravenously for 11 days. The total dose of tetracycline was 19 grams. Her BUN on admission was 35 milligrams percent. Two days later the BUN had risen to 67 milligrams percent, and the SGOT was 109 units. The patient had become comatose. By the third day the BUN had risen to 90 milligrams percent and continued to rise during her course in the hospital, ultimately to 162 milligrams percent. Total serum protein gradually declined to a total of 3.9 grams percent. Calcium declined

to a low of 6.7 milligrams percent. Phosphorus levels rose to a high of 12 milligrams percent. She developed a thrombocytopenia with platelet counts as low as 6,000 to 10,000 per cubic millimeter. Serum bilirubins gradually rose to 5.2 milligrams percent. Melena developed. She died 14 days after admission.

The autopsy revealed a pelvic abscess adjacent to the cervix which had drained spontaneously into the endocervical canal. The sections of liver showed fine, panlobular fat vacuolization characteristic of tetracycline toxicity. Sections of kidney revealed changes compatible with healing acute tubular necrosis. There were also moderate numbers of crystalline casts within the renal tubules. Other autopsy findings included acute pancreatitis, acute ulcerative duodenitis, and focal areas of mucosal hemorrhage in the small bowel.

Tetracycline assay of a specimen of serum obtained a few days prior to death revealed a blood level of 58 micrograms per milliliter by a microbiologic assay and 75 micrograms per milliliter by a chemical assay.

Comment

This patient was seriously ill to begin with, and glomerular filtration was undoubtedly diminished during the period of shock, which in turn probably caused some tubular dysfunction. As in the other cases the tetracycline administered could not be properly excreted and so built up to toxic levels, causing further renal damage and having toxic effects on the liver. The demonstration of pancreatitis at autopsy has also been a frequent finding in other reported cases of tetracycline toxicity, as has also been true of the mucosal hemorrhages and erosions noted in the gastrointestinal tract.

Case 4

The patient was a 59-year-old woman who entered the hospital with signs and symptoms of a pelvic abscess secondary to a perforation of a small bowel. Surgical drainage of the abscess and resection of a segment of bowel were performed. The patient received a total of 9.5 grams of tetracycline intravenously over a seven-day period. Bilirubin became elevated to 9.6 milligrams percent; blood urea nitrogen rose from 16 milligrams percent to 55 milligrams percent. The patient died on the sixth postoperative day.

The autopsy revealed characteristic hepatic changes of tetracycline toxicity. There was also a pre-existing portal cirrhosis with ascites. Moderate numbers of crystalline casts were present in the renal tubules, as well as minor, nonspecific, tubular changes.

Case 5

The patient was a 61-year-old man who had an obstructing small bowel carcinoma complicated by metabolic alkalosis and associated with slight elevation of blood urea nitrogen to 40 milligrams percent. At operation, the neoplasm was found to be nonresectable and was treated by a surgical by-pass procedure. The patient received 16 grams of tetracycline intravenously over a seven-day period. He developed evidence of gastrointestinal bleeding and died seven days postoperatively. Shortly before death, blood urea nitrogen was reported as 44 milligrams percent.

The body appeared jaundiced at autopsy. There was a primary adenocarcinoma of the jejunum. The liver showed characteristic panlobular fat vacuolization. Kidney sections revealed minor, nonspecific, tubular changes. No intratubular crystals were present.

Case 6

The patient was a 69-year-old woman who died five days after cholecystectomy and partial pancreatectomy for cholelithiasis and chronic pancreatitis. She received 11 grams of tetracycline over a five-day period. Blood urea nitrogen increased from 6 milligrams percent preoperatively to 32 milligrams percent on the day of death.

The autopsy revealed the typical histologic changes of tetracycline-induced fatty liver. Sections of kidneys revealed nonspecific tubular changes. No intratubular crystals were present.

Case 7

The patient was a 79-year-old woman who developed an acute cholecystitis. Treatment consisted of parenteral fluids and a total dose of 9 grams of tetracycline in six days. She developed jaundice, gastrointestinal bleeding, and progressive azotemia. She died six days after the onset of symptoms. Blood urea nitrogen reached a level of 117 milligrams percent shortly before death.

The autopsy revealed cholelithiasis and common duct stones. Erosion of the common duct by a stone led to perforation of the duct and bile peritonitis. There were hemorrhagic erosions of the stomach, small bowel, and colon, as well as a pancreatitis. Sections of liver showed the characteristic changes of tetracycline toxicity, and there were large numbers of crystalline casts within the tubules.

Summary of Pathologic Findings

Liver

Grossly, the livers of the affected patients were not enlarged, ranging in weight from 1,295 grams to 2,100 grams. The livers of four patients appeared pale, suggesting fatty change grossly. One patient had grossly demonstrable cirrhosis. The most characteristic microscopic appearance was fine, foamy, fat vacuolization of liver cell cytoplasm (Figure 1). The appearance differed markedly from

the large fat vacuoles encountered in the usual fatty liver and in association with various types of liver injury. The fat vacuolization was not associated with evidence of intrahepatic bile stasis, liver cell necrosis, or inflammation. The fatty change appeared to develop first in the central portion of the lobule and was restricted to the centrilobular area in one patient. However, in the other six patients the fatty change was panlobular in distribution.

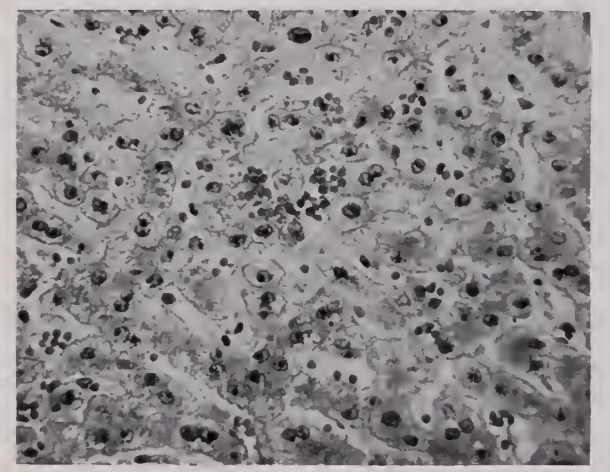


Fig. 1—Fine, foamy vacuolization of liver cell cytoplasm characteristic of tetracycline toxicity. Hematoxylin and eosin. Magnification approximately × 100.

Kidneys

The renal lesions associated with tetracycline were much less characteristic. There were varying degrees of swelling of tubular epithelial cells, but no fat was demonstrated in the tubular cells by means of fat stains. Occasional tubules contained eosinophilic protein casts. The lumens of other tubules contained small numbers of desquamated, degenerated, tubular epithelial cells. The kidney tubules of five of the seven patients contained spherical crystals which varied in color from yellow-brown to yellow-green and had both radial and concentric striations. These crystals were birefringent when viewed under polarized light, and by this technique the striated character of the crystal was readily demonstrated (Figure 2). The smaller crystals averaged 10 to 15 micra in diameter. The larger crystalline masses completely filled the tubular lumens and were often fractured by the microtome knife incident to the preparation of sections (Figure 3). By means of fluorescent microscope examination, the crystals were found to exhibit a brilliant yellow to green fluorescence.

Intratubular Crystals

"Leucine-like" intratubular crystals of this type have been described in the kidneys of some patients in whom tetracycline toxicity has been demonstrated.[8,11,12] The nature of these crystals is not known. It has been assumed that they are probably leucine crystals reflecting liver damage due to tetracycline. However, the fluorescence of this crystalline material suggests that possibly tetracycline or a fluorescent degradation product of the drug is incorporated in this crystalline material. Additional studies are being performed to characterize the precise nature of this crystalline material. The intratubular crystals were present in the majority of the patients and provided an additional histopathologic characteristic indicative of tetracycline toxicity. There appeared to be a rough correlation between the degree of azotemia and the number of intratubular crystals present. Crystalline material was present in large amounts in patients who

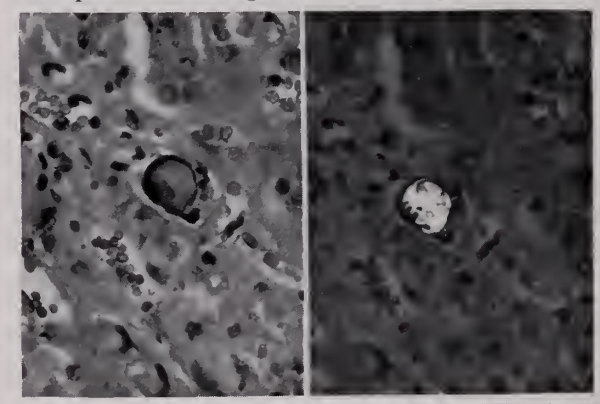


Fig. 2—Crystalline material within renal tubules showing appearance under regular illumination, and characteristic birefringence when viewed under polarized light. Magnification approximately × 450.

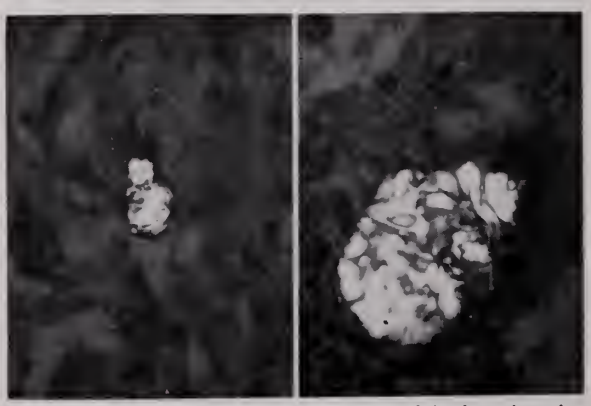


Fig. 3—Birefringent crystalline material viewed under polarized light, illustrating variation in size and appearance. Magnification approximately × 450.

had high blood urea nitrogen levels, and was infrequent or absent in patients in whom blood urea nitrogen levels were not greatly elevated.

Pancreas

Acute pancreatitis, which has been described as a manifestation of tetracycline toxicity in some patients, was encountered in two of the patients in this series. The mechanism by which the drug produces pancreatic injury is unknown. In some of this group of patients there was evidence of hemorrhagic manifestations. Impaired synthesis of blood coagulation factors by the liver may have contributed to these hemorrhagic manifestations.

Discussion

With the increasing number of reports of cases of hepatorenal failure associated with increased tetracycline serum levels, a rather characteristic clinical picture has begun to evolve. Often the patient who develops hepatorenal failure attributed to tetracycline toxicity is one who already has a variable degree of chronic or temporary renal insufficiency. The causes of the chronic renal insufficiency seen in these cases have been quite variable and may be related to pyelonephritis, polycystic kidneys, or nephrosclerosis. Temporary types of renal insufficiency are such as may be seen in bacteremic shock or hypovolemic shock. Almost all of the cases reported have received tetracycline intravenously.

Glomerular Excretion

Tetracycline is excreted mainly by glomerular filtration, and it appears that even small reductions in glomerular filtration may lead to rapid build-up of tetracycline levels in the blood. Blood levels of 40 to 80 micrograms per milliliter may be obtained, substantially higher than the usual therapeutic levels of 1 to 5 micrograms per milliliter. High levels of tetracycline in the blood have a toxic effect on the renal tubules; renal insufficiency with progressive azotemia and hyperphosphatemia is then produced. Urinary output is characteristically not reduced, and the patients may produce rather large quantities of isothenuric urine.

Hepatotoxic

High levels of tetracycline in the blood also have a toxic effect on the hepatic cells, with the manifestations of hyperbilirubinemia, elevated SGOT, prolonged prothrombin time, and hypoproteinemia.

Metabolic Affection

Hyponatremia and hypokalemia may also be present, probably due to an increased fecal excretion of sodium and potassium. Calcium levels in these patients may become quite low, probably related to hypoproteinemia as well as to the hyperphosphatemia that ensues. These patients develop a metabolic acidosis related to both the hepatic and renal insufficiency. The CO_2 combining power may become quite low. Lactic acidosis has been described and may possibly be related to the anti-anabolic effect of tetracycline on protein metabolism. The cause of the frequent finding of gastrointestinal ulcers and erosions and pancreatitis is not definitely known. It seems likely, however, that this too represents a cellular toxic effect of tetracycline.

Pathogenesis of Clinical Syndrome

Tetracycline in high doses appears to exert an inhibitory effect on enzyme systems, and the most pronounced clinical effects are reflected in the liver and kidneys. Figure 4 illustrates schematically the probable pathogenesis of the clinical syndrome. Alteration of enzyme systems concerned with the excretion of bile leads to jaundice. Impairment of protein-synthesizing enzymes within the liver produces several effects. Lipoprotein synthesis is impaired, leading to accumulation of triglycerides within the liver and accounting for the fine fat vacuolization of liver cells. Bleeding tendencies appear to be related to impairment in the synthesis of various plasma coagulation factors by the liver. Detailed coagulation studies were not available in the cases which we described, but plasma prothrombin time was prolonged in all of the patients in whom this test was performed. Impaired synthesis of plasma protein leads to marked, rapidly developing hypoproteinemia, which is characteristic of the syndrome.

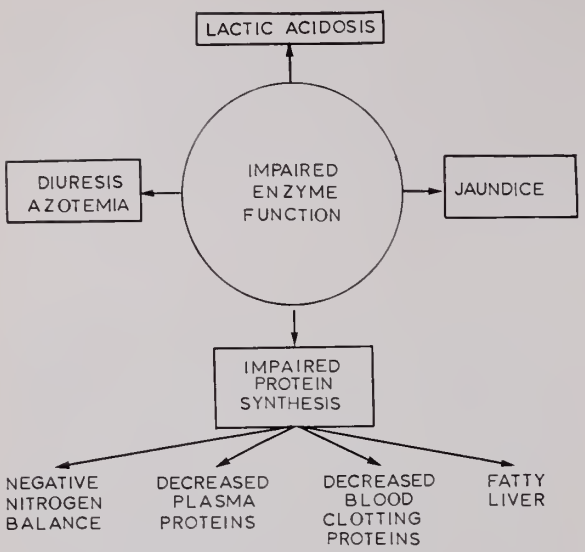


Fig. 4—Pathogenesis of clinical syndrome of hepatorenal toxicity due to tetracycline.

The pathogenesis of the azotemia due to tetracycline is not clearly defined. Several mechanisms may be operative. It has been postulated that the azotemia may be related indirectly to the impairment of protein synthesis. Because of the inability of hepatic protein-synthesizing enzymes to incorporate amino acids into tissue protein, the amino acids are catabolized to urea and other end-products, leading to negative nitrogen balance and an increased load of nitrogenous substances which must be excreted by the kidneys. This increased excretory load of urea and other nitrogenous substances may exceed the kidneys' excretory capacity. Tetracycline has also been shown to have a diuretic effect by promoting excretion of salt and water, tending to produce dehydration and augmenting the azotemia. However, the drug probably also has poorly understood direct effects on enzyme systems and tubular transport mechanisms within the renal tubular epithelial cells.

It should be noted that the vast majority of cases reported so far are female, and many of these are in pregnant females. In one case report of hepatorenal toxicity in a male, the man was receiving estrogens for a prostatic carcinoma and had had a previous orchiectomy. Three of the seven cases reported in this paper are in males, all elderly and 61, 77 and 87 years old respectively. One may raise the question as to whether androgens have any protective role in preventing the development of tetracycline toxicity.

Although many of the cases reported have shown some degree of pre-existent temporary or chronic renal insufficiency, some have not. In these cases it seems that the high dose level provided by intravenous tetracycline alone was sufficient to cause hepatorenal toxicity. In most of these cases the doses of intravenous tetracycline exceeded the recommended 2 grams per day given intravenously. There have been occasional cases reported, however, where the 2-gram daily intravenous dose was not exceeded and in which there was no evidence of pre-existent renal insufficiency. One case has been reported where the patient did not receive any parenteral tetracycline but received only oral tetracycline in doses of 1 gram daily for twelve days. This was a pregnant woman with hypertension. The BUN prior to the initiation of therapy was not mentioned; therefore the possibility of mild renal insufficiency prior to therapy cannot be excluded. It is noted that in cases reported where the dose of tetracycline has not exceeded 2 grams and where there has not been a prior renal insufficiency, streptomycin has been used concomitantly. This raises the question of a possible effect on the renal tubules by streptomycin as well as by tetracycline.

Prognosis

The prognosis for patients who develop tetracycline hepatorenal toxicity is almost uniformly fatal. Only a few patients have survived; in these the diagnosis has been quickly suspected and the doses of tetracycline have not been large. Tetracycline hepatorenal toxicity is therefore a serious problem even if infrequent. It may, however, be more frequent than has been heretofore recognized. Of our cases, in only Case 1 was the diagnosis made before death. Cases 2, 3, and 4 were diagnosed immediately at autopsy; but Cases 5, 6 and 7 were found only by a retrospective review of our autopsy files.

Conclusions

It would seem best to avoid giving tetracycline parenterally unless there is no other alternative. If so given the maximum safe dosage would seem to be closer to 1 gram daily than

to 2 grams. In fact, it appears certain that the dose of tetracycline given parenterally should never exceed 2 grams daily. If doses greater than 1 gram daily are to be given, frequent monitoring with tetracycline levels would seem to be prudent.

Tetracycline serum levels should never exceed 16 micrograms per milliliter.[14,15] One should avoid giving tetracycline by any route to patients with renal insufficiency unless there seems to be no other alternative. Further, care should be taken in administration of tetracycline to patients who have been in shock or who are dehydrated. Finally, one should refrain from the concomitant use of other potentially hepatotoxic or nephrotoxic drugs with a tetracycline drug.

Acknowledgments

Mr. A. C. Dornbush, Lederle Laboratories, Pearl River, New York, performed the microbiologic assays for tetracycline, and Dr. R. G. Kelly, also of Lederle Laboratories, performed the chemical assays. Dr. Edmond Yunis, Department of Laboratory Medicine, University of Minnesota Medical School, performed the fluorescent microscope studies of the kidney sections.

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Loss of Memory?

A middle-aged woman felt a bit under the weather, so she paid a visit to her doctor. "Well," he asked, "what seems to be the trouble?" "Doctor," she said, launching into a summary of her symptoms. "I have a general backache, shooting pains in my legs, and bilious attacks." "I see," said the doctor, busily taking notes. "How old are you?" he asked. "I'll be 31 next month," the patient answered coyly. "Hmmm," the doctor mused, adding another note. "Slight loss of memory, too."*

*Mark Wachs.

Don't expect applause. Deserve it.—Forbes Epigrams

A man's liver is his carburetor.—Author unidentified

Man's Oxygen Reserves

Professor Wallace S. Broecker*, Columbia University, maintains most convincingly that, though man's survival may ultimately be threatened by loss of his atmospheric oxygen, some other ecological retribution for man's abuse and plunder of his planet will doubtless overtake him long before his oxygen supply is irretrievably depleted. The myth of vanishing atmospheric oxygen, in the professor's opinion, has been created and nurtured by the news media alarmists, and not by reputable scientists like himself.

"If automobiles account for 50 percent of the total oxygen demand in an urban area, carbon monoxide would reach a critical level before the oxygen content of the air had dropped by 2 percent.

"If we continue to burn chemical fuels at our currently accelerating rate, then by the year 2,000 we shall have consumed only about 0.2 percent of the available oxygen. If we were to burn all the known fossil fuel reserve we would use less than 3 percent of the available oxygen. Clearly, a general depletion of the atmospheric oxygen supply by the consumption of fossil fuel is not possible in the foreseeable future."

Contamination of fresh-water lakes, rivers, and streams is a different matter, however, because the oxygen content therein can be so drastically reduced as to be insufficient to support and maintain the indigenous aquatic biota: that familiar food chain pyramiding from the lowly plankton up to the largest fishes and amphibia. And axiomatically, whenever and wherever there is interference with any area of the natural eco system, the total biosphere may be jeopardized.

As for salt water, on the other hand, Professor Broecker contends that were it possible to dump all of man's waste products into the ocean, "the oxygen supply in the deep sea would last 25,000 years."

*Editor's note: As Professor Broecker points out, we are faced with so many other more urgent environmental challenges to survival, e.g., overpopulation and the numerous other menaces to our furred and feathered fauna, that it would seem impolitic to raise the oxygen exhaustion bogyman at this time; and he anticipates hopefully that the popular press will soon bury the "bete noire" it has projected onto a credulous and needlessly apprehensive public. Important however, as a sense of perspective and an awareness of priorities may be, would not abiding interment of the oxygen exhaustion bogy be equivalent to the mythical ostrich ploy for evading issues? After all, in the span of eternity 25,000 years is but a moment of time; so had we not better mark well the "mene tekel" on the wall and take heed for future generations, lest 26,970 A.D. be that oft-prophesied Doomsday?**

*Science, 168:1537 June 1970

Full Circle

To rise over the disappointment of a moment is one of the signs of progress toward maturity. An assistant found Thomas Edison one morning at 2 o'clock, wreathed in smiles. Expecting that Edison had solved the problem in research he had been carrying on for years, the assistant said: "You've solved it! you've found the answer?" And Edison said: "Not a blamed thing works: now I can start over again."*

*M. Dale Baughman: Treasury of Stories.

Acid-Base Balance Abnormalities in Respiratory Therapy

JOSEF K. WANG, M.D.*

THE MAIN PURPOSE of respiratory therapy is to restore to normal the body's chemistry following abnormal alveolar ventilation or hypoxemia. Any degree of deviation in alveolar ventilation results in abnormal blood gases and these, in turn, cause acid-base balance abnormalities. Therefore, knowledge of acid-base physiology is essential to an understanding of the principles of respiratory therapy.

Alveolar ventilation (V_A) and CO_2 production (V_{CO_2}) determine the alveolar and arterial CO_2 tension (P_aCO_2). A simplified relationship is expressed in the following equation:

$$P_aCO_2 \propto \frac{V_{CO_2}}{V_A}$$

This indicates that the arterial CO_2 tension is directly proportional to CO_2 production and inversely proportional to alveolar ventilation.

Alveolar Hypoventilation

A decrease in alveolar ventilation relative to CO_2 production results in hypercapnia,† hence respiratory acidosis. The change in blood pH may be ameliorated first by buffer reactions occurring in the blood, then by the renal mechanism. As the result of buffer reactions, there is a slight increase in the HCO_3^- concentration and a large increase in the H^+ concentration. The blood buffer mechanism is demonstrated in the following reactions:

$$CO_2 + H_2O \rightarrow H_2CO_3$$

$$H_2CO_3 + Buf^- \rightarrow H\,Buf + HCO_3^-$$

where the symbols H Buf and Buf^- are weak, acid and conjugated forms of the non-bicarbonate buffer system. In vivo, HCO_3 formed in a buffer reaction may shift from the vascular space into the extravascular space;[1] therefore, plasma HCO_3^- concentration rises less at a given elevation of pCO_2 than is the case in vitro. Applying various diagrams[2,3,4] derived from in-vitro studies to observe data may lead to small errors in the interpretation of acid-base measurements. Actual in-vivo studies made it possible to construct the "significance band" which represents the range of 95% of the observations.[5,6] Only the values above or below this range signify the likely possibilities that body HCO_3^- is in fact increased or decreased. For clinical purposes, however, the possible errors of using the diagrams derived from in-vitro studies may not be critical.

If pCO_2 remains elevated, an increased renal H^+ excretion and HCO_3^- generation will take place as a compensatory mechanism. With moderate levels of elevated pCO_2 the pH is often in the normal range; with high pCO_2 values (> 80 mmHg) some degree of acidosis is uniformly present. As CO_2 production exceeds ventilation the alveolar accumulation of CO_2 displaces oxygen. To predict this effect the following equation is accurate enough for most clinical purposes, assuming the subject is breathing air, in a resting state at sea level,[7]

$$P_AO_2 = 150 - 1.25\ P_aCO_2$$

when P_AO_2 is the alveolar oxygen tension. This reduction of alveolar oxygen tension is frequently accompanied by an increased alveolar-arterial O_2 difference in patients with advanced respiratory disease and is likely to be at least 15 mmHg in patients in respiratory failure.

One can predict that a patient in respiratory failure with a P_aCO_2 of 80 mmHg, for example, will have a P_AO_2 of 50 mmHg ($150 - 1.25 \times 80$) and a P_aO_2 of 35 mmHg ($50 - 15$). Such acute, profound hypoxemia due to hypercapnia frequently leads to lactic acid formation. As the renal compensatory mechanism takes place, renal HCO_3 generation is increased

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†See Test Your Word Score, page 973.

and the plasma Cl^- concentration is reduced to the same extent to maintain the electroneutrality. There is also evidence that acute hypercapnia is accompanied by a negative K^+ balance.[8]

During acute transient hypercapnia, adequate respiratory assistance can restore the normal P_aCO_2 and pH values. If respiratory assistance fails to improve alveolar ventilation THAM (Tris hydroxymethyl amino methane) may be helpful as a temporary measure for correcting the acidosis. THAM or sodium bicarbonate can also be given in a complicating metabolic acidosis secondary to hypoxemia. In chronic respiratory insufficiency accompanied by metabolic alkalosis, the restoration of a normal blood chemistry is slow, requiring also a profound readjustment of the renal acid-base regulation and time to reach a new electrolyte balance. A sudden improvement of alveolar ventilation may result in a severe alkalosis and its complications. Administration of the reabsorbable anions, such as Cl^-, not only improves the HCO_3^- excretion but also permits the restoration of normal potassium balance. It appears that a *gradual* increase of alveolar ventilation accompanied by administration of KCl and careful estimation of acid-base balance and electrolytes is quite important in treating chronic respiratory insufficiency. A rapid reduction of P_aCO_2 may also have deleterious effects on the central nervous system. In chronic hypercapnia cerebrospinal fluid HCO_3^- is elevated to keep pace with the rise in cerebrospinal fluid pCO_2, thus maintaining cerebrospinal fluid pH close to normal. A sudden fall in arterial pCO_2 due to mechanical ventilation causes cerebrospinal fluid pCO_2 to drop due to its rapid equilibration with blood but leaves an uncompensated HCO_3^- excess, hence, an alkalosis of the cerebrospinal fluid which tends to reduce cerebral blood flow. Carbonic anhydrase inhibitors, such as Diamox (Acetazolamide), inhibit the converson of carbonic acid to carbon dioxide. Diamox, by inducing a cerebral carbonic acidosis, can be used to prevent the alkalosis of cerebrospinal fluid. It also provides for an increased stimulation of the pH-sensitive respiratory central chemoreceptors.[9,10]

Alveolar Hyperventilation

An increase in alveolar ventilation relative to CO_2 production causes hypocapnia, hence, respiratory alkalosis. A reduction in the renal tubular hydrogen ion secretion and an increased bicarbonate concentration in the urine partially restore the pH towards a normal value. However, the contribution of the renal mechanism to the compensation for respiratory alkalosis is of little quantitative significance.[11] A simultaneous mild metabolic acidosis develops, due to the rise in blood concentration of lactic and pyruvic acids in response to the reduction in PCO_2.[12] When large increases in lactate and pyruvate occur in association with hypocapnia and alkalosis it becomes necessary to look for some metabolic or circulatory disturbance as a contributing factor.[13] It has been suggested that the process of compensation for respiratory alkalosis is a pathologic state characterized by progressive loss of bicarbonate.[14] Elevated blood acidity may stimulate the respiratory center, leading to further hypocapnia, and the development of a vicious circle. Although there are relatively few precise studies regarding in-vivo response of blood to a loss of CO_2, a 95% significance band has been constructed.[15]

In a state of uncomplicated respiratory alkalosis, restoration of p_aCO_2 by centrally-acting respiratory depressants or by muscle relaxants and controlled ventilation is probably preferable to the administration of CO_2-enriched inspired air. Replacement of existing bicarbonate deficit may be the initial therapeutic measure, if a complicating metabolic acidosis exists.

Summary

Knowledge of acid-base physiology is of great help in the management of the clinical course.

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Mules kick. Who wants to become known as a mule.—Forbes Epigrams

Neoplasms of the Brachial Plexus

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J. GRAFTON LOVE, M.D.† and MALCOLM B. DOCKERTY, M.D.‡

PRIMARY NEOPLASMS of the brachial plexus are uncommon. Godwin[1] reported 11 cases involving schwannoma of the plexus, and Ehrlich and Martin[2] included a few cases involving brachial plexus tumors in their report of schwannoma in the head and neck. A single case report appears in the recent English language literature.[3] Neurologic findings may be meager, a mass may be biopsied or removed without the suspicion that it is a nerve tumor, and the results of ill-advised surgery may be disastrous. Thus it seems worthwhile to review the Mayo Clinic cases involving neoplasms of the brachial plexus.

Material and Methods

The case records, surgical reports, pathologic material, and follow-up reports on patients with primary or local neoplasms of the brachial plexus seen at the Mayo Clinic during the 20-year period 1948 through 1967 were reviewed. There were seven patients with benign neoplasms and the stigmata of von Recklinghausen's neurofibromatosis (Table 1); three with malignant neoplasms and the stigmata of von Recklinghausen's neurofibromatosis[4] (Table 2); 14 with solitary neurofibromas or schwannomas and no other stigmata of von Recklinghausen's neurofibromatosis (Table 3); two with miscellaneous benign neoplasms (Table 4); and two with miscellaneous malignant neoplasms (Table 5).

Results

Twenty-eight patients with primary brachial plexus neoplasms were seen during the 20-year period. Nine had either multiple skin or subcutaneous stigmata or multiple neurofibromas of nerves and were judged to have von Recklinghausen's neurofibromatosis. Two of these patients had neurofibrosarcomas that terminated fatally despite surgery. The remaining seven had benign tumors (one with a schwannoma and six with neurofibromas). As might be anticipated, there was a tendency for the same or other nerve tumors to cause further significant disability in these patients.

Fourteen patients had solitary benign nerve tumors without general stigmata of von Recklinghausen's neurofibromatosis. Ten of these tumors were neurofibromas and the remaining four, schwannomas. These patients had little tendency toward recurrence of the tumors; in general the results of surgery were excellent. The ten patients with neurofibromas could well be suspected of having von Recklinghausen's disease. Because no other stigmata were noted however, we grouped them separately.

Two of the three patients with miscellaneous benign tumors did very well. One patient recovered deltoid function after removal of a lipoma. The inclusion of a desmoid "tumor" in a series of neoplasms might be questioned. Somewhat surprisingly, this patient did very well and was without evidence of recurrence after four years. Interestingly, another patient with a desmoid tumor involving the brachial plexus who was operated on at our institution before the time of this series also had an excellent result, with no evidence of recurrence

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‡Mayo Clinic and Mayo Foundation, Section of Surgical Pathology.

TABLE 1
Patients With Benign Neoplasms and the Stigmata of von Recklinghausen's Neurofibromatosis

Sex and age, yr.	Presenting signs and symptoms	Type of surgery	Pathologic diagnosis	Neurologic status		Follow-up
				Preop.	Postop.	
F, 49	Rt arm pain, 3 yr; 2 previous tumor removals	Excision, 2 tumors, sensory branches in axilla and supraclavicular	Neurofibroma	Normal	Normal	Recurrence, 4 yr
M, 25	Weak rt hand and foot when 16 yr of age; tumors rt C-6 and lt C-7 removed; postoperative x-ray therapy; recurrence when 24 yr of age	Cervical laminectomy and meningocele repair, no intraspinal tumor; tumor of lower trunk rt brachial plexus removed	Neurofibroma	Moderate weakness of rt arm and leg; extensor plantar responses	No change	Progressive rt hemiparesis (?radiation myelopathy)
F, 17	Multiple skin tumors; mass rt axilla, 1 yr; local pain	Total removal, large tumor involving medial brachial and antibrachial cutaneous nerves	Neurofibroma	Normal	Subjective numbness	No recurrence of tumor July 1968 and no further neurologic defect
M, 30	Mass rt axilla, with shooting pain, 5 yr	Removal, multiple tumors of rt brachial and cervical plexus over 9 yr	Neurofibroma	Normal	Normal	Progressive arm and chest pain, 3 percutaneous cordotomies done elsewhere without relief
F, 19	Multiple tumors; large mass rt axilla; café-au-lait spots	Excision, large tumor of rt brachial plexus	Schwannoma	Normal	Normal	No change, 3 yr
M, 25	Multiple skin tumors; large rt supraclavicular mass, with pain down arm	Removal, 3 large tumors of rt brachial plexus	Neurofibroma	Moderate weakness rt biceps brachioradialis, severe weakness right triceps	Normal	Unable to work 5 yr later because of tumors in rt neck
F, 31	Numbness, lt arm; lt supraclavicular mass; café-au-lait spots	Multiple tumors lt brachial plexus, one removed	Neurofibroma	Normal	Mild weakness brachioradialis, triceps, wrist extensors	Progressive weakness of extremity July, 1968, presumably due to growth of other tumors involving brachial plexus

TABLE 2
Patients With Malignant Neoplasms and Stigmata of von Recklinghausen's Neurofibromatosis

Sex and age, yr.	Presenting signs and symptoms	Type of surgery	Pathologic diagnosis	Neurologic status		Follow-up
				Preop.	Postop.	
M, 19	Rt supraclavicular mass; previous biopsies elsewhere; grade 2 neurofibrosarcoma; pain, lt shoulder; multiple skin tumors and café-au-lait spots	Subtotal removal, tumor of lt brachial plexus	Grade 3 neurofibrosarcoma	Moderate weakness, rt biceps, triceps, and wrist extensors	No change, pain decreased	Died 6 mo later of neoplasm
M, 36	Pain, lt arm; operated neurofibrosarcoma 3 yr before; recurred, reoperated and x-ray therapy; recent weakness, lt arm; multiple skin tumors and café-au-lait spots	Lt forequarter amputation; subtotal removal, tumor of rt brachial plexus	Grade 3 neurofibrosarcoma	Severe weakness of arms, bilateral	Rt arm unchanged	Died 9 mo later of hemorrhage from neoplasm

TABLE 3

Patients With Solitary Neurofibromas or Schwannomas and No Other Stigmata of von Recklinghausen's Neurofibromatosis

Sex and age, yr.	Presenting signs and symptoms	Type of surgery	Pathologic diagnosis	Neurologic status		Follow-up
				Preop.	Postop.	
M, 49	Asymptomatic mass, lt axilla explored elsewhere; no biopsy	Total removal, tumor lt brachial plexus	Neurofibroma	Normal	Normal	No change in condition, July 1968
M, 35	Numbness lt digits 4 and 5, 5 yr	Total removal, tumor from medial cord lt brachial plexus	Schwannoma	Minimal hypesthesia digits 4 and 5	No change	Doing well 1 yr postop.
M, 45	Mass, rt neck; schwannoma removed elsewhere, with profound weakness of rt upper extremity postop.	Removal, large tumor from roots of rt brachial plexus	Schwannoma	Profound weakness rt shoulder and arm	No change	No recurrence 2 yr postop.; weakness only moderate now
M, 36	Rt supraclavicular mass; biopsy elsewhere, neurilemmoma; superior mediastinal mass on x-ray	Thoracotomy and removal of substernal goiter; complete removal of tumor from brachial plexus	Schwannoma	Normal	Slight weakness rt triceps and hypesthesia digits 1, 2, and 3	Improved with "excellent recovery, as strong as preop. and playing tennis," slight numbness, rt index finger and half of thumb and middle finger, 1968
M, 16	Aching lt arm and tingling digits 2 and 3; mass above clavicle	Removal, tumor of lt plexus; hemorrhagic recurrence removed 3 mo later	Neurofibroma	Moderate weakness of pectoralis major, biceps, wrist flexors, and digit extensors	First operation, weakness decreased; second operation, weakness slightly worse	Only minimal weakness biceps and deltoid 3 yr later; no recurrence
M, 72	Flashes of "hot" pain down rt arm; mass, upper medial arm	Total removal, encapsulated tumor of rt brachial plexus	Schwannoma	Normal	Normal	Good health, 2 yr later
M, 49	Mass, lt neck 6 mo, with tingling into arm on pressure	Biopsy by general surgeon, then total removal of tumor from roots of plexus	Neurofibroma	Normal	Severe weakness biceps, triceps, deltoid, and brachioradialis	Weakness decreased moderately 1 yr later; can get hand to mouth
F, 62	Asymptomatic, rt supraclavicular pressure produced pain in elbow	Total removal, tumor rt C-7 root	Neurofibroma	Normal	Normal	Weakness of intrinsic hand muscles, 5 yr later; exploration revealed only scarring
F, 68	Lt supraclavicular mass; operation elsewhere, followed by "burning" in hand	Total removal, tumor lt C-8 root	Neurofibroma	Moderate weakness, all muscles lt upper extremity	Slight increase in weakness	Burning pain, entire arm; high cervical cordotomy and lt sensory rhizotomies without relief; frontal lobotomy done elsewhere with relief
F, 33	Pain neck, rt shoulder and arm; tightness of legs	Laminectomy and removal of C-6 intradural dumbbell tumor, followed by removal of intra- and extraforaminal tumor 3 mo later	Neurofibroma (?Dejerine - Sotas in 2nd spec.)	Spasticity of legs	Severe weakness of muscles supplied by rt C-5 and C-6 roots	No change in 17-yr follow-up

TABLE 3 (Cont.)
Patients With Solitary Neurofibromas or Schwannomas and No Other Stigmata of von Reklinghausen's Neurofibromatosis

Sex and age, yr	Presenting signs and symptoms	Type of surgery	Pathologic diagnosis	Neurologic status		Follow-up
				Preop.	Postop.	
F, 34	Mass, rt axilla with shooting pain medial forearm; biopsy elsewhere	Total excision, tumor rt medial antibrachial cutaneous nerve and medial cord of plexus	Neurofibroma	Subjective hypesthesia, rt medial forearm	Objective hypesthesia, medial forearm	Good functions and doing office work
F, 37	Mass rt axilla; neurofibroma removed elsewhere with complete postop. Radial palsy	Resection, traumatic neuroma junction, posterior cord, and radial nerve, with anastomosis	Traumatic neuroma, initially neurofibroma	Complete rt radial palsy after initial surgery	No change	Good triceps and wrist extension 1 yr later
F, 63	Palpable rt supraclavicular mass, with pain in shoulder and arm; two operations elsewhere for neurofibroma, with profound postop. weakness	Exploration: extensive trauma and scarring upper trunk of plexus, no repair; no tumor recurrence		Complete paralysis, rt arm and shoulder except for wrist and finger flexors	No change	July 1968, relief of pain and return of elbow flexion and some return of elbow extension
F, 51	Mass beneath outer 1/3 of left clavicle	Total excision of tumor from lateral cord lt brachial plexus, preserving all but one fascicle	Neurofibromas	Normal	Normal	No recurrence; asymptomatic

TABLE 4
Patients With Miscellaneous Benign Neoplasms

Sex and age, yr.	Presenting signs and symptoms	Type of surgery	Pathologic diagnosis	Neurologic status		Follow-up
				Preop.	Postop.	
F, 54	Mass, rt axilla	Lipoma removed from axilla by general surgeon with transection of axillary nerve; resutured by neurosurgeon		Subjective weakness of arm	Complete deltoid paralysis	Recovery of deltoid function
F, 49	Lt supraclavicular mass, with aching in arm	Tumor displacing brachial plexus removed	Desmoid	Normal	Minimal weakness of subscapularis and infraspinatus	No recurrence 4 yrs; minimal paresthesia
M, 41	Lt supraclavicular mass since childhood; pain in forearm, digits 1 and 2; operated elsewhere, 11 yr before for ganglioneuroma	Exploration and removal of tumor and nerve to infraspinator	Neuroma; review original tissue, ganglioneuroma	Weakness lt infraspinators	No change	Incurred pain without evident anatomic basis

after 33 years.

The two patients with malignant neoplasms but no stigmata of von Recklinghausen's disease both died; however, the patient with a neurofibrosarcoma lived for seven years after operation. An argument could be raised for including this case with the von Recklinghausen's cases.[5]

Discussion

Palpable Brachial Plexus Mass

This review revealed several points that deserve emphasis. Any patient who complains of shooting or burning pain in the upper extremity or of paresthesia or other symptoms suggestive of irritation of the nerve or nerve root should have careful palpation of the course of the brachial plexus and its terminal nerves. If a brachial plexus tumor is present, a palpable mass frequently can be detected (21 of the 28 cases in this series). Even if a mass is not present, palpation in the region of the tumor may elicit typical nerve pain or paresthesias, giving an important clue to the correct diagnosis. The need for thorough preoperative and postoperative neurologic evaluation is obvious.

Neurosurgical Procedure

Sixteen of the 28 patients underwent surgical exploration, biopsy, or attempted tumor removal before the definitive neurosurgical procedure, either by surgeons at other institutions or in several instances by general or orthopedic surgeons in our clinic. In four instances, attempted removal of benign tumors produced severe and probably unnecessary neurologic deficits. A neurosurgeon experienced in this type of peripheral nerve surgery can frequently remove benign tumors by splitting uninvolved nerve fascicles with only minimal, if any, postoperative increase in neurologic deficits. If there is suspicion that a tumor in the region of the brachial plexus involves nerves, the initial surgery should be done by a neurosurgeon. If at operation a surgeon inexperienced in this type of surgery encounters a tumor involving nerves, he probably should terminate the operative procedure and refer the patient to a neurosurgeon rather than risk unnecessary neurologic deficit.

Evaluation of Malignant Tumors

Malignant peripheral nerve tumors are associated with a poor prognosis.[6] In this series, all patients with these tumors died from the tumor. Attempt at local resection is doomed to failure. If operation is to offer any chance of a cure for malignant nerve tumors, it must be done early and be extensive. In brachial plexus tumors, this probably means radical forequarter amputation, for even if extensive local brachial plexus surgery were successful, as is very unlikely, it would usually leave the patient with a useless extremity. Recommending such radical surgery is a problem that must be thoroughly explored in each individual case by the surgeon and the patient. The need for absolute accuracy in the pathologic diagnosis of

TABLE 5
Patients With Miscellaneous Malignant Neoplasms

Sex and age, yr.	Presenting signs and symptoms	Type of surgery	Pathologic diagnosis	Neurologic status		Follow-up
				Preop.	Postop.	
M, 54	Severe pain, digits 1 and 2 rt hand; myelogram, negative; decompression rt C-6 root done elsewhere, pain worse	Infiltrating tumor of rt plexus radically removed with nerve trunks	Grade 2 neurofibrosarcoma	Mild weakness, wrist extensors	Moderate weakness of biceps, wrist, and finger extensors; pain decreased	Pain recurred in 4 yr; weakness same, 6,000 R given; recurrence singularly removed; metastases present in both lungs 7 yr postop.
F, 20	Malignant hemangiopericytoma removed from lt brachial plexus elsewhere; postop. irradiation	Resection of recurrent infiltrating tumor of brachial plexus	Grade 3 malignant neoplasm, probably hemangiopericytoma, lymph nodes involved	Profound muscle weakness lt arm	No change	Died of metastases 3 mo after second operation

these rare malignancies before performing such radical surgery is obvious.

Terminology of the benign nerve tumors has been a source of great confusion and argument for years. In this review we have followed the general concepts of terminology and classification used by Russell and Rubinstein.[5] The term "schwannoma" has been used in preference to neurilemmoma because, as Russell and Rubinstein have noted, the tumor is a multiplication of cells rather than a membrane, and also because the distinctive term may prevent some of the confusion that arises when the term "neurilemmoma" is used. We believe that the schwannoma usually can be differentiated from the neurofibroma by its morphologic features, although an occasional tumor may share features of both lesions and both lesions may have the same principal cell of origin.

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We Seek Authority

In addition to a craving for magic there is another tendency which affects us all; to seek security in authority. There are some things about which it is too painful to be in doubt. Certainty is sought in authority, without too critical an enquiry into the source of that authority. This tendency has repeatedly asserted itself in the history of medicine and has frequently delayed its progress. The authority of Aristotle, Galen, and the Church have each in their own way been detrimental in this respect. Whereas Hippocrates placed reliance on general methods, Galen exalted the importance of drugs, a fact of which the term "Galenicals" still reminds us. Galen departed from the simplicity of Hippocrates and evolved such subtle and complicated theories, such definite and artificial classifications that the original doctrines were almost lost sight of, especially in therapeutics. Not only so, but the medieval mentality, always subservient to authority, elevated Galen's writings to the level of papal infallibility, to question which was blasphemy. Only among the Arabs and at Salerno in Italy was the torch kept feebly burning. It required the sceptical inquiring mind of the Renaissance, the rebirth of the Greek spirit, in fact, to fan that torch into flame again.*

*Sir Walter Langdon-Brown: Thus We Are Men, 1969.

Editor's Note: Somewhat analogous to creating an image of infallibility.

When age comes on, men get sadder and wiser, but women get sadder and wider.—Zula Greene



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Indications—Essential hypertension; edema or ascites of congestive heart failure, cirrhosis of the liver and the nephrotic syndrome; idiopathic edema. Some patients with malignant effusions may benefit from Aldactone, particularly when given with a thiazide diuretic.

Contraindications—Acute renal insufficiency, rapidly progressing impairment of renal function, anuria and hyperkalemia.

Warnings—Potassium supplementation may cause hyperkalemia and is not indicated unless a glucocorticoid is also given. Discontinue potassium supplementation if hyperkalemia develops.

Usoge of ony drug in women of childbeoring age requires thot the potential benefits of the drug be weighed agoinst its possible hazards to the mother and fetus.

Precautions—Patients should be checked carefully since electrolyte imbalance may occur. Although usually insignificant, hyperkalemia may be serious when renal impairment exists; deaths have occurred. Hyponatremia, manifested by dryness of the mouth, thirst, lethargy and drowsiness, together with a low serum sodium may be caused or aggravated, especially when Aldactone is combined with other diuretics. Elevation of BUN may occur, especially when pretreatment hyperazotemia exists. Mild acidosis may occur. Reduce the dosage of other antihypertensive drugs, particularly the ganglionic blocking agents, by at least 50 per cent when adding Aldactone since it may potentiate their action.

Adverse Reactions—Drowsiness, lethargy, headache, diarrhea and other gastrointestinal symptoms, maculopapular or erythematous cutaneous eruptions, urticaria, mental confusion, drug fever, ataxia, gynecomastia, mild androgenic effects, including hirsutism, irregular menses and deepening voice. Adverse reactions are infrequent and usually reversible.

Dosage and Administration—For *essential hypertension in adults* the daily dosage is 50 to 100 mg. in divided doses. Aldactone may be combined with a thiazide diuretic if necessary. Continue treatment for two weeks or longer since an adequate response may not occur sooner. Adjust subsequent dosage according to response of patient.

For *edema, ascites or effusions in adults* initial daily dosage is 100 mg. in divided doses. Continue medication for at least five days to determine diuretic response; add a thiazide or organic mercurial if adequate diuretic response has not occurred. Aldactone dosage should not be changed when other therapy is added. A daily dosage of Aldactone considerably greater than 75 mg. may be given if necessary.

A glucocorticoid, such as 15 to 20 mg. of prednisone daily, may be desirable for patients with extremely resistant edema which does not respond adequately to Aldactone and a conventional diuretic. Observe the usual precautions applicable to glucocorticoid therapy; supplemental potassium will usually be necessary. Such patients frequently have an associated hyponatremia—restriction of fluid intake to 1 liter per day or administration of mannitol or urea may be necessary (these measures are contraindicated in patients with uremia or severely impaired renal function). Mannitol is contraindicated in patients with congestive heart failure, and urea is contraindicated with a history or signs of hepatic coma unless the patient is receiving antibiotics orally to "sterilize" the gastrointestinal tract.

Glucocorticoids should probably be given first to patients with nephrosis since Aldactone, although useful for diuresis, will not directly affect the basic pathologic process.

For *children* the daily dosage should provide 1.5 mg. of Aldactone per pound of body weight.

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References: (1) Sand, R.X.: New York St. J. Med. 61:2598-2602, 1961: (2) Renner, M.J., et al.: Hosp. Topics 39:71-73, 1961: (3) Haas, J., and Kay, L.L.: Southwest. Med. 42:30-32, 1961: (4) Marshall, W.: Clin. Med. 7:499-502, 1960: (5) Strauss, B.: Clin. Med. 4:307-310, 1957.

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Editorials

Hospital Infections*

MANY STUDIES, papers, and discussions on nosocomial† infection have been recorded. For many years the staphylococci were notorious for the role they played in infections of this type. More recently, gram-negative organisms have assumed an increasingly important role in hospital infections. Since the organisms responsible for these infections have changed over the years, it seems reasonable to predict that they will continue to change in the years to follow. Not only do groups of nosocomial organisms change but, in addition, individual organisms change their characteristics. This is particularly true regarding their sensitivity to the various antibacterial drugs.

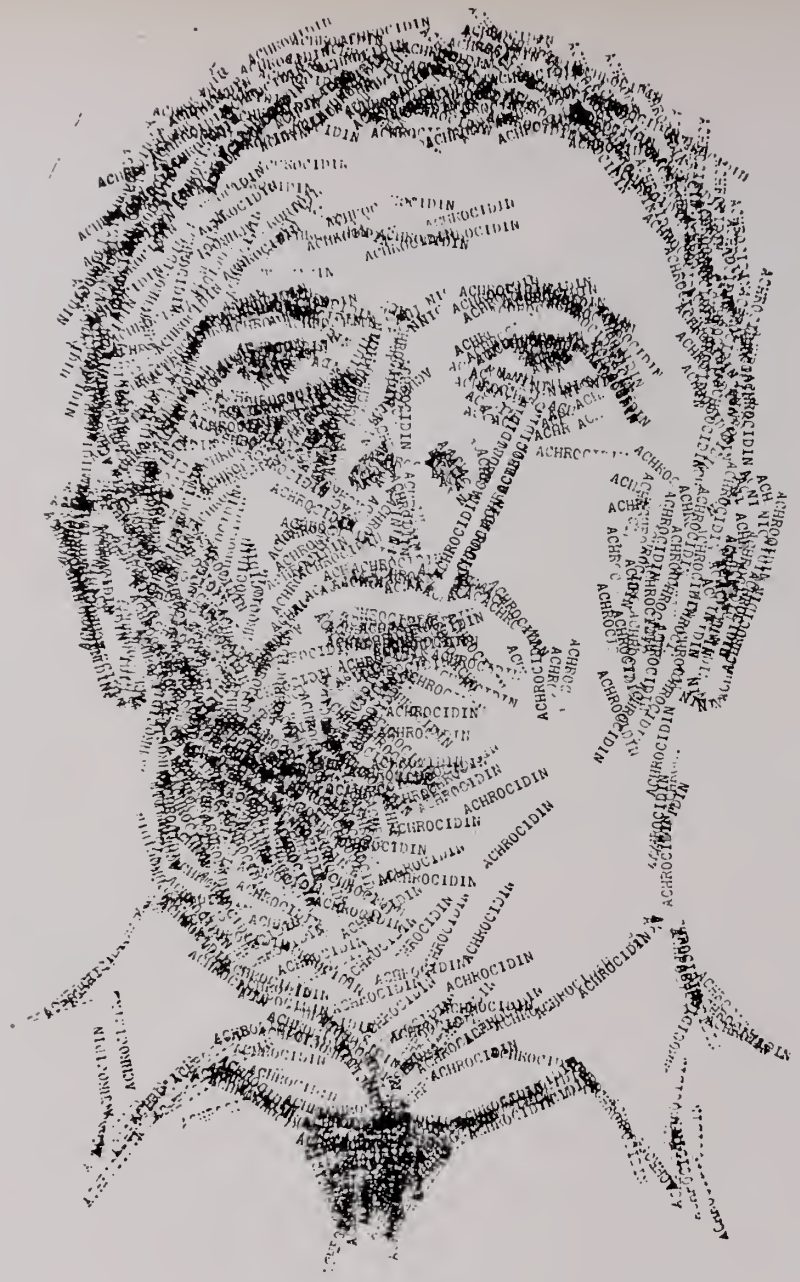
In the past, studies of these organisms have been hampered because of the difficulties in accumulating and processing the vast amount of data essential to the documentation of changing patterns in organisms and their characteristics. With the advent of machines capable of rapid data processing and retrieval, investigations similar to that reported by Dexter and Bates have become possible. I am certain that the future also holds simpler and more rapid methods of determining antibiotic sensitivities which will further facilitate the rapidity with which this information will become available.

Most clinicians interested in infectious diseases recognize the importance of nosocomial organisms and the diseases with which they are associated. In the light of past experience and present knowledge, it seems reasonable to assume that this problem will continue and likely become more severe. The use of cytotoxic agents and immunosuppressives and the implantation of foreign material continues to increase. These are but a few of the factors that tend to increase hospital infections. It is my hope that there will be an ever increasing number of studies relating to this problem. Comprehensive and current investigation is essential to keep the clinician informed concerning the prevalence of hospital infections, the organisms responsible, and their antibiotic sensitivity patterns. This knowledge will be most helpful in the selection of the best treatment program for the control of these infections.

William E. Wellman, M.D.
Rochester, Minnesota

*Dexter, J. F., and Bates, H. A.: Antibiotic Sensitivity Patterns of Staphylococcus and Gram Negative Bacteria. Minnesota Med 53:205, 1970.

†See Test Your Word Score, Page 973.



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Warning: In renal impairment, since liver toxicity is possible, lower doses are indicated; during prolonged therapy consider serum level determinations. Photodynamic reaction to sunlight may occur in hypersensitive persons. Photosensitive individuals should avoid exposure; discontinue treatment if skin discomfort occurs.

Precautions: Drowsiness, anorexia, slight gastric distress can occur. In excessive drowsiness, consider longer dosage intervals. Persons on full dosage should not operate vehicles. Nonsusceptible organisms may overgrow; treat superinfection appropriately. Treat beta-hemolytic streptococcal infections at least 10 days to help prevent rheumatic fever or acute glomerulonephritis. Tetracycline may form a stable calcium complex in bone-forming tissue and may cause dental staining during tooth development (last half of pregnancy, neonatal period, infancy, early childhood).

Adverse Reactions: *Gastrointestinal*—anorexia, nausea, vomiting, diarrhea, stomatitis, glossitis, enterocolitis, pruritus ani. *Skin*—maculopapular and erythematous rashes; exfoliative dermatitis; photosensitivity; onycholysis, nail discoloration. *Kidney*—dose-related rise in BUN. *Hypersensitivity reactions*—urticaria, angioneurotic edema, anaphylaxis. *Intracranial*—bulging fontanels in young infants. *Teeth*—yellow-brown staining; enamel hypoplasia. *Blood*—anemia, thrombocytopenic purpura, neutropenia, eosinophilia. *Liver*—cholestasis at high dosage.

Upon adverse reaction, stop medication and treat appropriately.

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The Role of Xenon-133 Technique in Assessment of Pulmonary Function *

THE EQUIPMENT required to assess pulmonary function by the xenon-133 technique is both complex and expensive and has little likelihood of finding its way into the average pulmonary function laboratory. However, it is likely that information from such studies may help identify heretofore unsuspected abnormalities in pulmonary function and suggest simple ways to quantify such abnormalities. A case in point stems from the study by Anthonisen and associates[1] of patients with mild chronic bronchitis who had normal ventilatory findings. Xenon-133 studies revealed decreased ventilation and depressed ventilation:perfusion ratios in some lung regions, especially the lung bases.

These patients also showed frequency dependence of lung compliance, a test that is simpler but does require an esophageal balloon and spirometer. Evidence has been presented suggesting that frequency dependence of compliance may be an early sign of peripheral airway disease.[2] The ability to detect early peripheral airway disease could be extremely important in epidemiologic studies evaluating chronic obstructive lung disease, air pollution, occupational lung disease, etc. Chances are good that from such leads even simpler tests not requiring an esophageal balloon may be developed to evaluate the small airways.

The above comments illustrate the important contributions that basic research can make to human health. It is important that the medical community draw the layman's attention to such accomplishments.

Robert E. Hyatt, M.D.
Rochester, Minnesota

*Tsai, S. H., Loken, M. K., Ponto, Richard, and Griswa, Philip: Pulmonary Function: A Study in the Baboon Using Xenon-133 and a Scintillation Camera. Minnesota Med 52:1893, 1969.

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President's Letter

(Continued from page 937.)

are underpaid and are becoming more militant and vociferous. Hospitals are ancient and dilapidated. In short, Britain's National Health Service is ailing.

We in the United States have inherited much knowledge from England in law, medicine, science, literature and the arts. Currently, most of the health-insurance plans being recommended by various organizations in the United States, including our federal legislators, are patterned in divers degrees after the English system. Should we now close our eyes to the manifest perils of a plan for national health care that has been tried for 22 years and is failing?

One can scarcely contest the notion that the American people, as represented by our federal government, have the prerogative, by means of that government, to create legislation to ensure that certain segments of our society deprived of medical care will receive it. Physicians recognize this; their major and certainly earnest concern is that they be consulted by, and allowed to give some counsel to, those who will fashion this important legislation.



Raymond J. Jackman, M.D., President,
Minnesota State Medical Association

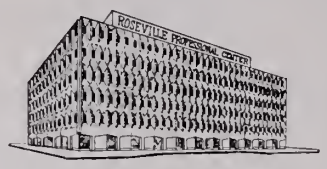
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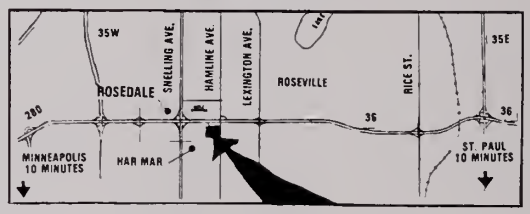
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Congenital Dislocation of the Hip

The optimal time for treatment in congenital dislocation of the hip is during the newborn period. With proper splintage of the hip in flexion and abduction, the primary laxity of the capsule diminishes within a few months, the hip becomes stable, the femoral head and acetabulum develop in a normal relationship to each other, and the child is cured. Taking advantage of such an ideal situation depends, obviously, on the clinician's ability to diagnose the instability of the hip joint as early in the infant's life as possible.

The Ortolani test (or Barlow's modification of it) demonstrates this instability by subluxing the femoral head in and out of the acetabulum. However, not all newborns in whom a positive Ortolani sign has been elicited within a few days after birth develop congenital dysplasia or dislocation; and conversely, not all newborns with acetabular dysplasia have enough capsular laxity to demonstrate subluxation of the femoral head over the edge of the acetabulum.

A second diagnostic test, that of eliciting limited abduction of the leg at the hip, is generally more accurate several weeks or months after birth—after adaptive contracture of the hip adductor muscles has occurred—than during the newborn period. Again, as with the Ortolani test, false-negative and false-positive results occur in the newborn period. However, if both the Ortolani test and the abduction test are done each time the infant is examined—not only during the newborn period but also at regular intervals during the first few months of life—very few abnormal hips will be overlooked.

Abnormalities in the hips of infants are difficult to detect roentgenographically. Roentgenographic evidence of lateral displacement of the femur or of a sloping acetabulum is of significance if the Ortolani test is positive or if abduction is limited. In this situation, the roentgenogram serves only as a confirmatory test. Roentgenography later becomes of real value in assessing the effectiveness of treatment, as evidenced by the development of the acetabulum and the capital epiphysis.

The presence of a persistently positive Ortolani test, or of a positive abduction test, in an infant with a normal-appearing hip roentgenogram presents a perplexing problem. In this situation, it is better to treat the lax joint capsule or the tight adductors with splintage for a few months than risk overlooking a potentially abnormal hip that may not become evident until the optimal treatment period has passed.

Anthony J. Bianco, Jr., M.D.
Rochester, Minnesota

*Babb, F., Beer, J., Soiseth, R., and Sundberg, B.: Congenital Dislocation of the Hip. Minnesota Med 53:15, 1970.

Test Your Word Score

Hypercapnia—*excess carbon dioxide in the blood* (page 957)

Nosocomial—*relating to a hospital* (page 969).

Stent—*a device used to maintain a bodily orifice or cavity during healing* (page 996).

Dermatoglyphics—*surface markings on the palmer regions* (page 1005).

Dysesthesia—*impairment of any of the senses, especially of touch; or a painful and persistent sensation* (page 1012)

You May Be Right

As I read the July number of MINNESOTA MEDICINE, I was enjoying, as always, the attractive cover and arrangement of material; the practical and well-written articles; and the many personal comments, opinions and quotations that make the magazine so attractive.

To myself I was saying 'thank-you to you' and thinking of saying so in a letter. Then comes the editorial, "If Dr. Hippocrates Calls," etc., and I realize how near we could be to losing this choice magazine.

I cannot think of any way to increase the budget and support MINNESOTA MEDICINE, but I can do what I set out to do—thank you most heartily for what you have given me throughout the years.

Olga Hansen Litzenberg, M.D.
Minneapolis, Minnesota

Editor's Note: For the increase in your annual dues to $125.00 not one cent goes to the budget of MINNESOTA MEDICINE. *If we receive the subscription price we run in the black.*

I understand, through the grapevine, that we will be seeing smaller amounts of you and less often in the future. I would like to register a very large and loud objection to having our one intellectual outlet cut off by a small group at the state meeting. I realize that funds are in short supply and there should be some economizing made and I suggest that economy start at the top and not down where our reading material is.

There is a page in MINNESOTA MEDICINE that tells all about the officers, councilors, consulting editors, associate editors and contributing editors and general manager—I would like to see somebody's salary cut, but I don't know which fellow to jump. I will miss you.

Elizabeth B. Jerome, M.D., F.A.A.P.
Minneapolis, Minnesota

P.S. I found Jane Hodgson's article in your July issue expressed my thoughts exactly and I would like to add my name to the long list of people who are behind her. In my office not one week goes by that we don't see a child that no one wants, but the mother is usually stuck with it. Where are those voices who shout therapeutic abortion is murder. The emotional murder of these youngsters after arrival in our society and the future of our society is going to be a very sad situation.

I greatly admire the way you are running the MINNESOTA MEDICINE Journal and I assure you of my support in any way possible.

Colin Markland, M.D.
Minneapolis, Minnesota

I cannot close this letter without mentioning that I thoroughly enjoy every single issue of MINNESOTA MEDICINE which I always read from cover to cover and which I consider one of our best publications.

Kurt Schnitzer, M.D.
Santa Ana, California

The Editor's Soliloquy

Looking Backward from the Twenty-first Century

DURING THE LATTER decades of the Twentieth Century we of the medical establishment exploited to the utmost our elite professional image and the honorable tradition that had endowed us with an enviable status of independence, authority and integrity. We thereby unwittingly forfeited those values to pernicious politico-legal-socioeconomic machinations, but deluded ourselves that our noble calling was being stultified by the dictates of an autocratic Federal Government, when maybe it was we ourselves who had forced the Administration to intervene in our affairs on behalf of the Nation's ill. For it found us so involved in self-induced bureaucracy and internecine struggle that we could scarcely continue private practice in our traditional humanitarian and altruistic manner.

Unfortunately, it was the vociferous few among us who were responsible for this debacle by over-ruling the apathetic majority and influencing the voting delegates to numerous unwise decisions that culminated in our collapse.

As a result of our heedlessness we found ourselves mired down in the bureaucratic red tape of thousands of committees and resolutions monopolizing the time and energy of our local, state and national organizations: a vicious cycle originally instituted and later implemented for the very purpose of keeping the Federal Government off our back and out of our hair.

But we failed! Government fiat invaded our domain notwithstanding our heroic efforts to exclude it. It proceeded to dictate to us and to attempt to enforce policies calculated to keep us in line: to polish up our tarnished image and restore public confidence in our competence and dedication. The result? Further paralyzing bureaucratization!

The individual practicing physician, no matter what his specialty, faded away into a large group where patients entered with a number and, after three or four days, were cranked out, so to speak, emerging with a diagnosis, a half-dozen prescriptions, and a mimeographed routine to be followed. The treatment of organic disease was directed by a set of typewritten rules and regulations.

Patients with functional ailments gravitated to the quacks and charlatans where they could expect more individual consideration and a chance to get things off their chests. Psychiatric patients had to attend group sessions because no psychiatrist was sufficiently interested, under Federal aegis, to deal with individual patients. Nor did he have the time.

The patient's record was clear, substantive, and properly punched for the Utilization IBM machine because the system required proof that the doctor had discharged his assigned responsibility. The physician needed this substantiation in the event of litigation, for, regardless of what any patient or interested witness might testify to, the record would speak for itself. Ex cathedra! In fact, the cost of litigation insurance often exceeded the annual income of most doctors: an ironic paradox due to the rapacious demands of plaintiffs, their attorneys, and their doctors. Almost all diseases and all symptoms had been declared by categorical Supreme Court decision to have been caused by incidents, accidents, or other doctors; for these remuneration became the only cure.

The patient with a surgical problem learned with resignation to assume his place on the waiting list according to the lettered severity of his disease. The patient awaiting less urgent and more elective surgery often carried his waiting list number to his grave, having died of natural causes* before his turn came up.

Organ transplantation had become commonplace, and it was not unusual to observe at the demise of one of these multiple transplant individuals a battery of legal counsel waiting at hand, each to claim for his client his share of the inheritance which had accumulated from the generous donations of previous heirs and sympathizers.

Individuals with mechanical hearts, vinoplastic vessels, synthetic lungs, metabolic livers and dialyzing kidneys formed exclusive clubs of their own that arrogantly violated civil rights by excluding robots from their organizations.

Consultations were stored in magnetic-tape bins and could be dialed on a closed circuit. New telephonic devices had been invented so that the consultant could interrupt the canned consultee by dialing an additional number, provided he could interpret the key. The dialogue-cum-repartee sounded humorously and reminiscently like a shouting match on Echo Rock in the Valley of the St. Croix.

The population had become static; eugenics was practiced, and only rarely were a man and woman allowed to use their own seed, though donors for the eugenics bank were at a premium. A genetic throw-back occurred just often enough to intimidate most couples from petitioning to produce more than their stipulated allotment of two offspring. However, an occasional religious fanatic proved sufficiently recalcitrant to insist on three in order to gain greater assurance of entering the Kingdom of the Hereafter; for do not the Scriptures adjure man: Be fruitful and multiply?

Also an occasional long-haired, bewhiskered, tattooed and bauble-bedecked old-timer would nostalgically reminisce about the days of Old Doc Hess when a man and a girl could be left alone with their own instincts.

Carl O. Rice, M.D.

*Old age.

OLD DOC HESS SAYS: Don't let frustrations take the fun out of your work.—C.O.R.

Miracles of Surgery

Francisco Arceo

The same surgeon restored other gravely injured patients; a man, gored by a bull, whose face was split from ear to ear; another slashed by a sword so that his nose and upper jawbone had fallen to his chin and the severed features were cold and almost dead by the time the surgeon arrived. Proper stitching and bandaging restored both men's faces so that little trace remained of their injuries.*

*The Patient's Progress by Felix Mart-Ibanez, 1962.

Editor's Note: I expect that the surgeon dictated a bit more in his operative notes than actually existed. It is a pretty modern dictum, however, that "you can't go back of the record."

B-D

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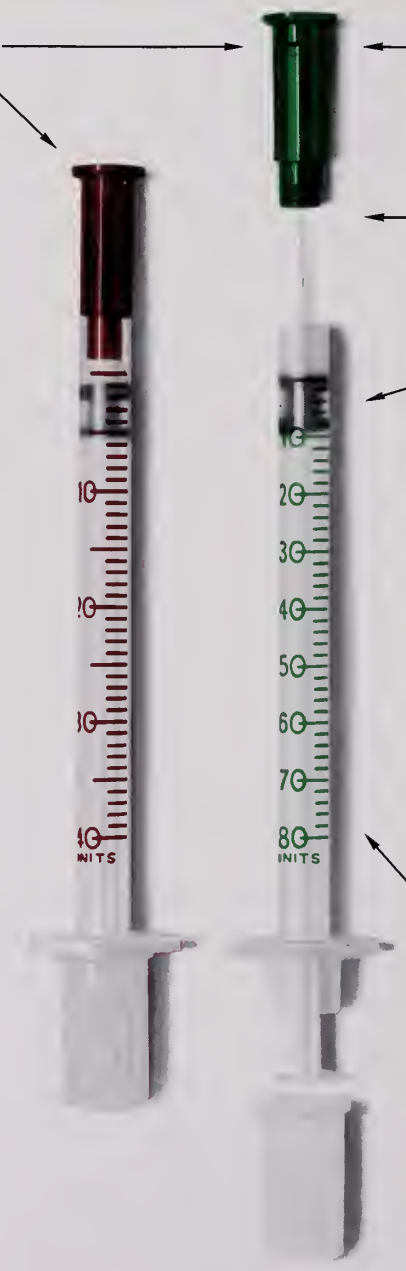
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Curbstone Consultation

RECONSTRUCTIVE SURGERY

QUESTION: What are the indications for referring patients for reconstructive surgery in arterial occlusive disease of the lower extremities?

ANSWER: A patient should be considered as a potential candidate for reconstructive surgery if he has severe calf claudication which incapacitates him in carrying out his work or essential activities, if he experiences severe ischemic rest pain in the involved extremity, or if early gangrenous changes have occurred in the foot or toes. Patients with symptoms referrable to one or more of these categories comprise the pool of potential candidates for reconstructive arterial surgery. The final selection of any given patient for surgery, however, must await the outcome of a femoral arteriogram. This diagnostic study is done to determine whether or not an adequate distal runoff exists. Although a single open artery is sufficient to proceed with reconstructive surgery, the chances of achieving success will vary directly with the number of patent branches at the popliteal trifurcation.

Some surgeons feel it is permissible to forego a femoral arteriogram in those instances where amputation is the alternative to a reconstructive procedure. Under these circumstances the runoff distally can be checked at the time of surgery by an arteriotomy in the popliteal artery and noting the degree of backflow. If backflow is insufficient to permit reconstructive surgery, then amputation is carried out. It is my personal feeling that femoral arteriography should be secured whenever possible, either at the time of surgery or beforehand, to take advantage of the more quantitative information which it can provide.

Harold D. Kletschka
Montgomery, Alabama

An Apple A Day

A young doctor and a young dentist shared the services of a receptionist and both fell in love with her.

The dentist was called away on business, so he sent for the receptionist and said: "I am going to be away for ten days. You will find a little present in your room."

She went in, and found ten apples.*

*Financial Post (Toronto)

Historic Hospitals

First Hospital in the New World
Hospital of San Nicolás de Bari, Santo Domingo



Ruins of the Hospital of San Nicolás de Bari, Santo Domingo. Courtesy Instituto Cultural Dominico-Americano.

Christopher Columbus, on his second American voyage, founded the first Spanish colony in the New World on the northern coast of the island of Hispaniola. He named the city Isabela in honor of the queen. After further exploration, he returned to Spain, leaving his brother, Bartholomew, in command of the colony.

The site was poorly suited for a city, and in 1496 Bartholomew had to move the colony to a new place on the southern shore, Nueva Isabela, now the city of Santo Domingo and capital of the Dominican Republic. Still the colony failed to thrive, and because of many disappointments, including inept administration by the Columbus brothers, King Ferdinand and Queen Isabela appointed a new governor in 1501, Don Nicolás de Ovando.

Among the many instructions which the sovereigns gave the new governor was one requiring him to see that the people be provided with hospitals in which the poor, both Christian and Indian, could be cared for. Accordingly, in 1503 Governor Ovando founded the Hospital of San Nicolas de Bari in Santo Domingo. The hospital was supported by the governor and other royal officials and by the alms of colonists and outsiders. It was constructed of perishable materials and had a capacity of only six beds in the beginning. By 1508, Ovando had founded two other hospitals in the island's interior.

Early records of the hospital are fragmentary, as most of them were destroyed during the pillaging of Santo Domingo by Francis Drake's privateers in 1586. It is known, however, that an addition to the San Nicolas Hospital was begun about 1533 and was completed in 1552. Fever patients were moved into the new building while trauma cases and other patients remained in the old. In 1541, the hospital affiliated with the Order of the Holy Spirit headquartered in Rome.

The third phase of construction, and the most important from an architectural point of view, began in 1553. It was a large stone structure, built on a cruciform foundation and resembling hospital buildings in Spain. This building was used for more than two hundred years, was repaired in 1789, but by 1821 was in ruins.

Warren L. Kump, M.D.
Minneapolis, Minnesota

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Fracture Conference

Internal Injuries Associated with Fractures*

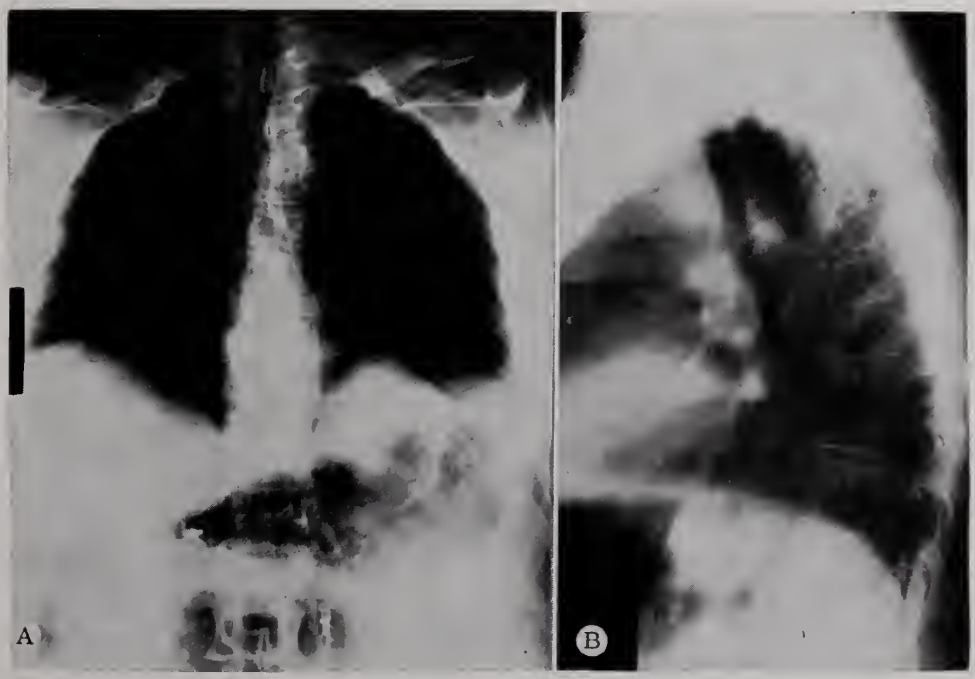
ASSOCIATED WITH fractures and accidents are injuries to the soft tissues—internal injuries that present diagnostic problems and injuries with which the orthopedist should have some familiarity.

Case 1

Dr. Vu V. Nguyen:

The first case of soft-tissue injury is that of a 34-year-old man who fell 30 feet from a ladder. He suffered compression fractures of the thoracic spinal column, left clavicle, left scapula, and sternum.

*Fracture Conference, September 9, 1968.



Figure—Anteroposterior (*A*) and lateral (*B*) views of thoracic spinal column and thorax, showing fracture of left scapula and compression fracture of T-4 and T-8 sustained 11 months before.

Dr. Einer W. Johnson, Jr.:

The roentgenogram of the chest shows an old fracture of the scapula (Figure, A) and irregularity of its axillary border. A compression fracture of the lower thoracic spinal column is also visible (Figure, B).

Dr. Nguyen:

These x-rays were taken when the patient was first seen here in July 1968 about 11 months after the injury. While the patient was hospitalized after the injury, a systolic murmur was noted along the left border of the sternum but cleared a few weeks later. An electrocardiogram taken at that time showed flattening of the T waves. A ventricular septal defect possibly of traumatic origin was suspected, but the possibility was ruled out after cardiac catheterization. An angiocardiogram at our clinic on August 5, 1968, showed mild mitral insufficiency. The final diagnosis was mitral valve insufficiency probably due to traumatic rupture of the chordae tendineae.

Contusion of the heart may be overlooked in chest injuries because critical signs are usually not obvious.[1] The hemodynamic change associated with rupture of the ventricular septa, chordae tendineae, or valves is usually manifested by cardiac failure. Ordinarily, these injuries become obvious if they are suspected and a search is made. Cardiac contusion is a potentially serious injury and sometimes leads to death. It may exist after injury despite the absence of obvious chest injury.

Precordial pain is the most frequent symptom. It may be angina-like or may have the usual characteristics of thoracic pain associated with chest-wound injury. Most patients with myocardial contusions seem to have tachycardia. A friction rub can be heard over the precordium. The electrocardiogram has proved to be the most reliable diagnostic aid. Obvious abnormality may appear in 48 to 72 hours after the injury. Most suggestive are changes in the RS-T complex, with flattening or inversion of the T waves. These changes may be indistinguishable from those of myocardial infarction. Change in serum enzyme levels is not specific because these values may also be elevated in injuries of the bone, brain, liver, and lungs. The differential and leukocyte counts are usually elevated.

The most important aspect of treatment is avoiding drugs that may increase myocardial irritability and overloading the cardiovascular system with blood or fluids in an effort to correct the hypotension. The patient should rest in bed for two to four weeks. When the contusions of the heart are minor, clinical improvement and the return of electrocardiographic findings to normal usually occur within a month. Digitalis may be used if cardiac failure supervenes. The use of anticoagulants has been questioned because of the theoretic possibility of extending the region of myocardial damage.

Dr. Johnson:

Cardiac trauma and contusion are not as uncommon as is ordinarily believed. Serial cardiograms of all persons who are involved in head-on collisions probably would indicate that a high proportion of these persons suffer cardiac contusions and that some of those with cardiac trauma fail to survive. Recently, a young man was brought into our emergency room after having been struck across the chest by a chain while riding his motorcycle. This trauma ruptured one atrium. Incidentally, those who have a laceration of the atrium do well until placed in an upright position. The patient came into the emergency room in a violent, thrashing condition and in the early stages of shock. To obtain a better position for roentgenography, he was raised

to a sitting position on the cart in the x-ray room and promptly died. This is characteristic of lacerations of the atrium.

With lacerations of the ventricle, patients do not survive even long enough to be brought into the emergency room. But even a simple cardiac contusion, and, in this instance, rupture of the chordae tendineae, is a serious injury. Although orthopedists usually see patients with broken bones, they are often the first to see the injured person, and consequently must recognize when there is a ruptured spleen or viscera, a cardiac contusion, or other soft-tissue trauma that may or may not be associated with a fracture.

Case 2

Dr. Nguyen:

This young girl had a contusion of the kidney and a fracture of the distal portion of the radius, and her abdomen was rigid. Her abdomen was opened and 400 to 500 ml of whole blood were removed. She has done well since.

Case 3

Dr. Nguyen:

This 57-year-old woman was a passenger in a car that collided with a truck. She received first aid in the hospital near the site of the accident and was brought to our clinic about six hours later. She had fractures of the right patella and left ulna; she was pale and agitated, and her blood pressure on admission was 80 mm Hg systolic and 60 mm Hg diastolic. During the next hour, abdominal distention with tenderness developed over the lower part of the abdomen, with an absence of bowel sounds. There also was ecchymosis over the lower abdominal and iliac crest regions due to pressure from the seat belt. Laparotomy was done on the night of the accident, and about 1,500 ml of clotted blood were removed from the abdomen. The exploration revealed a large tear in the mesentery and a perforation of the small bowel about six inches proximal to the ileocecal valve. Also, a long loop of bowel was infarcted. The perforation was closed, and the region of bowel infarction was resected. She had no other visceral injuries in the abdomen, but a roentgenogram of the chest showed some effusion in the base of the right lung. The next day oliguria and acidosis developed. The blood pressure was very low and was maintained only by the administration of epinephrine. Cardiac arrest developed and the patient died suddenly 48 hours after admission.

This patient had had abdominal injuries from a seat belt. A research of the literature has revealed about 10 references to such injuries. More than one million persons in the United States are injured each year in automobile accidents, and about 50,000 die. The risk of death or injury in such an accident depends to a large extent on the frequency of ejection, this being determined by the severity of the accident and the seat position. The value of the safety belt in reducing the frequency and severity of injuries resulting from automobile accidents is well-documented and accepted. But it is also evident that the introduction of safety belts may increase the frequency of certain injuries, particularly those in the abdominal region. When a person wearing a seat belt is involved in an accident, most of the force exerted on the body is suddenly imposed on the pelvic region. Therefore, it is logical that the study of injuries from seat belts should focus on the lower abdominal region.

Only 19 cases involving injuries from safety belts have been reported: 11 in the American and eight in the foreign literature. The actual number could be far greater because many cases have not been reported. Table 1 lists the cases of abdominal injuries resulting from the lap-type seat belt. The sites of injury include the duodenum, pancreas, small bowel, colon, spleen, and a gravid uterus. Viscera injured by the loop-type shoulder belt include hepatic veins, kidneys, renal artery, spleen, and the liver (Table 2). Injuries from the shoulder belt were more severe than those from the lap-type seat belt, and the first three cases reported involve fatalities. The first patient reported by Engberg[9] died from shock on the operating table. The patient with rupture of the kidney and avulsion of the renal artery reported by Von Bahr and Eriksson[10] died of cardiac arrest on the way to the operating room. The third patient, who had injuries to the liver and spleen, died the day after the accident.

Visceral injuries also may be caused by another type of seat belt—the diagnonal safety belt. Recently in Sweden, Saldeen[11] reported three fatal cases in which there was injury from diagonal safety belts. One patient had fractured the occipital condyles, with a tear in the medulla oblongata, and two patients were decapitated.

The mechanism of abdominal injuries involves the braking force of the lap belt as it is applied suddenly to the abdominal wall. The intra-abdominal viscera are susceptible to injury. Depending on the position or change in position of the belt, all abdominal organs could be traumatized by direct violence, by shearing or torsion, or by entrapment. The combination of all of these factors is also possible and accounts for the complexity of lesions. The bowel is most frequently injured. Bursting injuries to the small bowel can be produced by direct violence over a distended loop or by entrapment, kinking of a short segment of bowel with production of a closed-loop obstruction, and perforation. The loop of bowel may be closed by kinking at two

TABLE 1
Soft-Tissue Injuries From Lap-Type Seat Belt During Accidents

Authors	Cases	Sites
Garrent & Braunstein[2]	1	Duodenum and pancreas
Tolins[3]	1	Proximal jejunum
Cocke & Meyer[4]	1	Ribs and spleen
Rubovits[5]	1	Gravid uterus
Kulowski and Rost[6]	1	Late intestinal obstruction
Williams and associates[7]	4	Small bowel and colon
Gerristen and associates[8]	2	Small bowel

TABLE 2
Soft Tissue Injuries From Shoulder-Type Belt During Accidents

Authors	Cases	Sites
Engberg[9]	1	Hepatic vein
Von Bahr & Ericksson[10]	4	
	1	Kidney
	1	Liver and spleen
	1	Kidney
	1	Liver

places or in one place and closed by trauma at the second place or by a double-action trauma in two places.

Injury to the small bowel and its mesentery is produced by direct violence or by entrapment with subsequent perforation. The deceleration force is applied directly to the small bowel. The small vessels on the mesenteric border are torn and a hematoma is produced. If the force is great enough, the mesentery is torn perpendicular to the intestinal wall. Considerable devitalization can occur, resulting in gangrene and perforation of the bowel. The colon may be injured in the same way as the small intestine. In addition, the omentum may be entrapped by the belt, and, as the deceleration force continues and the patient is flexed, the omentum man be avulsed from its attachment to the transverse colon.

Trauma to the duodenum and pancreas is an uncommon but serious injury that can result from a seat belt. The mechanism of production of this injury can be severe lateral flexion of the patient to one side at the time of deceleration, with a resultant shearing force acting on the duodenum and pancreas. Rib fractures also may occur. Splenic injury is frequently the result of direct violence from a poorly placed safety belt. The spleen can be shattered at the time of injury or may rupture within a few days or weeks later.

Although rupture of the urinary bladder by a safety belt has not been reported, it is entirely conceivable that if distended with urine, the bladder could easily rupture through its dome or base, especially when there is an associated pelvic fracture. Rupture of the gravid uterus is a rare injury; Rubovits[5] has reported one such case. The deceleration force absorbed by the lower uterine segment produced a tear in the wall of the uterus. The force was transmitted to the amniotic fluid, resulting in increased hydrostatic pressure and ejection of the fetus through the left uterine horn into the peritoneal cavity. Actually, the advisability of using a lap belt during late pregnancy is questioned by some.

The mechanism of production of injuries from shoulder belts is similar to that of lap-type belts. However, with the former, torsional forces probably have a more prominent role in the production of trauma. As the victim's torso is twisted over the belt, ribs are broken and the spleen, liver, kidneys, or thin vascular attachments are likely to be injured by this shearing force. In three cases of fatal neck injuries reported by Saldeen[11] in Sweden, the diagonal safety belt was used. Although effective in head-on collisions, diagonal belts involve a considerable risk in collisions in which the subject is thrown toward the side of the car where the high end of the belt is fastened and then ejected from the car through an inadequately locked door. The lower jaw may be temporarily caught in the belt, the edge of which may cause neck injuries and even decapitation.

Cases from the literature have revealed that early diagnosis and treatment are essential in the management of visceral safety-belt injuries. But the diagnosis may be difficult because of associated injuries or circumstances. Because of the rarity of visceral injury, the examining physician must maintain a high degree of suspicion concerning possible intra-abdominal injury. The circumstances of the accident should be obtained from the patient or ambulance personnel and should include the speed of the car, the direction of impact, the condition of the car, and the placement and type of seat belt.

Except for serious injuries that result in quick death, the initial symptoms and physical findings are usually minimal. External evidence of trauma con-

forming to the configuration of the safety belt is helpful in suspecting intra-abdominal injury. But the presence or absence of such evidence does not confirm or rule out intraperitoneal trauma, although its presence might be an indication for surgical exploration of the abdomen. Sometimes, signs of persistent shock that cannot be explained on the basis of the extent of the orthopedic injuries indicate visceral injuries. The changing clinical course, with increasing abdominal tenderness and gradual loss of bowel sounds, supplies evidence of intraperitoneal injury. Roentgenographic studies may be valuable in the diagnosis of ruptured bowel or gravid uterus. Peritoneal tap should be used when the diagnosis is questionable, but a negative result should not be interpreted as indicating absence of intra-abdominal injury. Sometimes only laparotomy and exploration will determine the correct diagnosis.

When applied properly, the safety belt should not come in contact with the abdominal viscera; it is a restraining device on the bony pelvis. When it has caused intra-abdominal injuries, it has usually been improperly applied.

Dr. Johnson:

In the three cases presented, all patients suffered internal injuries from accidents: one from a seat belt, one from a fall, and one from being thrown through the windshield of a car. Each had internal injuries that were not immediately recognized, although such recognition is possible when there is a high degree of suspicion. Diagnosis can be made relatively early if attention is given to details. A four-quadrant tap, for instance, in a patient in whom an abdominal injury is suspected is valuable. Or lavage of the peritoneal contents, with analysis of the aspirant, is worthwhile if there is doubt.

In defense of the seat belt, it is estimated that the seat belt saves 5,000 lives a year in the United States and that it has reduced the number of fatal accidents by 35%; some researchers in Sweden believe that seat belts have reduced the number of fatal accidents by 65%. However, the manner in which seat belts are worn is important. They should be cinched up tightly and placed across the bony pelvis and not across the middle of the abdomen. Of course, the orthopedist knows that injuries from seat belts are not limited to those of soft tissue but may involve fractures of the lumbar spinal column and the iliac wings.

Einer W. Johnson, Jr., M.D.*
Vu V. Nguyen, M.D.*
Rochester, Minnesota

*Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

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Still

Some men are born great, some achieve greatness and others just keep still.—Frank Hubbard

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Thrombus Formation on Polymeric Materials

III. Mechanism of Blood Coagulation

DOUGLAS A. OLSEN, Ph.D.;* JAMES L. HAYNES, M.S.* and
HAROLD D. KLETSCHKA, M.D.†

In the preceding articles* we have discussed blood-compatible surfaces. An unanswered question is that of the mechanism by which a surface is rendered inert or nonthrombogenic: a question of considerable importance in that once the mechanism is understood the results may be used to prevent or modify deleterious interactions between polymer surfaces and blood. In this section we discuss the mechanisms of blood coagulation as they are presently understood.

The process by which the escape of blood from the vascular system is arrested or prevented is known as hemostasis. For the normally functioning system, the physiological processes of spontaneous hemostasis adequately control bleeding from small blood vessels. When larger blood vessels, especially arteries, are involved, mechanical assistance is usually required.

The following phases are a part of normal hemostasis:[1] (1) vascular phase, (2) platelet adhesion, (3) blood coagulation, (4) clot retraction, (5) fibrinolysis, and (6) repair. Normal hemostasis is separated into these phases for convenience and clarity; however, this division is somewhat arbitrary with considerable overlap. While blood coagulation is the main topic here, the vascular phase, platelet adhesion and clot retraction are also discussed briefly below. Fibrinolysis is discussed at the end of the section and repair is beyond the scope of this discussion.

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‡See Parts I and II, July and August issues, pages 773 and 877 of Minnesota Medicine.
Reprints may be obtained at the end of this series from Dr. Olsen at 4106 Linden Hills Blvd., Minneapolis, Minnesota 55410.

Vascular Phase

Although its exact role is not completely understood, a structurally and functionally sound blood vessel is required for normal hemostasis. When the integrity of a blood vessel is broken, a local vasoconstriction occurs which is immediately followed by the accumulation of platelets at the wound. Blood escaping from a wound induces a constriction in other vessels over which it flows. This vascular constriction is probably due to local reflex action and, in part, to a humoral mechanism.

Platelet Adhesion and Clot Retraction

The following is a very much simplified summary of the mechanism of platelet adhesion and clot retraction:[1] Immediately following a break in the endothelium of a blood vessel, platelets collect in the wound forming a loose mesh which reduces the escape of blood. There is considerable evidence that calcium ions link the negatively charged platelets to the damaged cell. Further accumulation of platelets is associated with the release of adenosine diphosphate (ADP). (ADP causes rapid coagulation of platelets in vivo and in vitro.) The process through this point is reversible. Next, the platelets release a thromboplastic substance after losing their internal organelles, and extrude a retractile protein. This process is called viscous metamorphosis. The contractile protein, in the presence of glucose and adenosine triphosphate (ATP) draws together threads of fibrin in the clot retraction process

Protein Adsorption and Platelet Adhesion

The exact mechanism of platelet adhesion is not known; however, recent studies aimed at

identifying events which occur rapidly when blood contacts a foreign surface should help elucidate the mechanism.

Baier and Dutton,[2] using a combination of infrared reflection spectroscopy, ellipsometry, and contact angle measurements, have also studied the nature of the events occurring immediately after exposing foreign surfaces to fresh flowing blood. Their study showed that within the first 5 seconds after contact with blood leaving the juglar veins of lightly anesthetized dogs, germanium prisms were uniformly coated with strongly adherent proteinaceous films having an average optical thickness equivalent to two layers of stearic acid (approx. 50 Å) and having critical surface tensions (surface energies) of about 36 dyne/cm. A contact time of 60 seconds led to a less uniform coating of average optical thickness equivalent to five layers of stearic acid (approx. 125 Å), but with a similar infrared spectrum and surface energy. The reflection spectra were consistent with the presence of either alpha-helical or random-chain configurations, but not with the extended chain beta-structure for proteins. Films cast from purified fibrinogen on platinum foils gave similar spectra and exhibited similar surface energies. Baier and Dutton's observations are consistent with the hypothesis that initial adsorptive events are dominated by fibrinogen deposition. However, the participation of small amounts of lipid or other protein is possible.

The results of the foregoing study confirm and generalize the hypothesis that the initial event in the interaction of blood with foreign surfaces is the rapid deposition of strongly adsorbed protein films. The idea that the initially adsorbed layer is necessary for, or greatly influences, platelet adhesion in thrombus formation is supported by the "threshold" time of one to two minutes noted before platelets first deposit on foreign surfaces from fresh blood.[3,4] The high surface energy values obtained for adsorbed protein films indicate that high energy groups are available in the adsorbed protein. These should contribute to better adhesion of platelets which contact them.[5]

Salzman et al.[6] have shown that the adsorption of platelets by heparinized surfaces is strongly influenced by specific plasma proteins. The evidence suggests the need for a protein cofactor, perhaps as an intermediate, and fibrinogen seems particularly active in this role. The ability of albumin to reduce fibrinogen binding to heparinized surfaces may offer a clue to a method for minimizing or eliminating platelet deposition.

Recently, Vroman and Adams also conducted a study aimed at identifying rapid changes occurring at plasma-solid interfaces.[7] According to the results of their study, the sequence of events occurring on exposure of intact plasma to a wettable oxidized silicon surface appears to be: adsorption of fibrinogen; conversion of fibrinogen film by something intact in the plasma (other than factor XII); removal of some matter from the film by intact factor XII (directly or indirectly) and activation of factor XII. Their work implies the following. (1) When fibrinogen is adsorbed from the intact plasma, platelets will adhere to the film if immediate contact is made. (2) As long as the plasma is intact, it will convert the adsorbed fibrinogen to a form which will not attract platelets. (3) Some of the adsorbed film will be removed if factor XII is present. (4) Factor XII and possibly XI will be activated, and the plasma will lose the capacity to continually convert its own fibrinogen. (5) If the activated plasma now flows to new solid surfaces, it may deposit fibrinogen which can no longer be converted and which will remain able to make platelets adhere.

Blood Coagulation

Although blood coagulation has received more attention than any other phase of hemostasis, some aspects of its mechanism are still uncertain. The following discussion outlines the generally accepted views. The use of different terms by various investigators was undoubtedly one cause of confusion in this area. The adoption of an international nomenclature, as shown in Table I, has been helpful.[8]

Classical Theory

The first major advance in blood coagulation theory was the discovery that the addition of crude tissue extracts to blood greatly accelerated clotting. This discovery led at the beginning of the century to the classical theory of blood clotting with the reactions as shown

in Figure 1.[1,8]

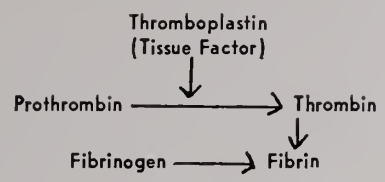


Figure 1

This theory was excellent and in its basic facts is as true today as it was ingenious nearly 70 years ago. The theory proposes a coagulable protein, fibrinogen and its product fibrin. Clotting is thought of as promoted by the activation of a clotting enzyme prothrombin and its product thrombin. The incoagulability of blood in vessels was thought to be due to the absence of tissue extracts in the blood.[8]

Mechanism of Blood Coagulation

The mechanism of coagulation is now known to involve the participation of several blood proteins (factors) which act alternately as substrates in the inactive form, and as enzymes in the active form. Coagulation involves a complex chain reaction (the "waterfall sequence") represented in Figure 2.[1,8,10]

TABLE

The International Nomenclature for Blood Coagulation Factors and Their More Common Synonyms[8]

Factor	Common Important Synonyms	Properties
I	Fibrinogen	Converted by thrombin to fibrin with the release of fibrinopeptides
II	Prothrombin	The precursor of thrombin adsorbed by $Al(OH)_3$ $BaSo_4$ and $Ca_3(PO_4)_2$ Not present in serum.
III	Thromboplastin Tissue factor	Present in saline extracts of most tissues, notable activity being present in lung and brain.
IV	Calcium	Required for the interaction of all clotting factors except XI, XII, and IIa.
V	Labile Factor Accelerator globulin	Not adsorbed by $Al(OH)_3$ $BaSO_4$, $Ca_3(PO_4)_2$. Not present in serum. Labile on storage. Required by extrinsic and intrinsic clotting.
VI	THIS TERM IS NOT NOW USED	
VII	Stable Factor. Serum accelerator globulin. Autoprothrombin I. Proconvertin.	Adsorbed by $Al(OH)_3$, $BaSO_4$ and $Ca_3(PO_4)_2$ Present in serum. Stable on storage. Not involved in intrinsic clotting.
VIII	Antihaemophilic Factor A Antihaemophilic globulin	Not adsorbed by $Al(OH)_3$ $BaSO_4$, $Ca_3(PO_4)_2$ etc. Absent from serum.
IX	Autoprothrombin II Antihaemophilic Factor B Christmas Factor Plasma thromboplastin component	Adsorbed by $Al(OH)_3$ $BaSO_4$, $Ca_3(PO_4)_2$ etc. Present in serum.
X	Stuart-Prower Factor Autoprothrombin III	Adsorbed by $Al(OH)_3$ $BaSO_4$, $Ca_3(PO_4)_2$. Present in serum.
XI	Plasma thromboplastin antecedent (PTA) factor	Adsorbed by glass and celite, sodium stearate etc. Not adsorbed by $Al(OH)_3$ $BaSO_4$. Present in serum.
XII	Hageman Factor	Adsorbed by glass and celite, sodium stearate etc. Not adsorbed by $Al(OH)_3$ $BaSO_4$. Present in serum.
XIII	Fibrinstabilising factor Fibrinase	Required for the formation of cross linkages in fibrin during the conversion of fibrinogen to fibrin by thrombin.

where the suffix "a" indicates the active forms of the factors. Phospholipid, possibly of platelet origin, may be required at the reactions noted. Calcium is required at all stages.

At least 10 proteins play a role in normal blood coagulation. Nine of these are important in coagulation promoted by contact with glass and are probably involved in coagulation triggered by other surfaces. These proteins have been established as separate entities by the existence of human mutants who lack, on an inherited basis, the ability to synthesize one of them. They have been assigned Roman numerals until the chemistry and mode of catalysis are better understood. Several of them have been substantially purified. Experiments with purified preparations indicate that they interact in pairs. Thrombin (activated Factor II) converts fibrinogen (Factor I) to fibrin by controlled partial proteolysis; the same mechanism probably operates in the conversion of Factor IX to activated Factor IX by activated Factor XI. Similarly, partial proteolysis is probably the mechanism whereby thrombin converts Factor XIII to activated Factor XIII. Activated Factor XIII converts fibrin from a urea-soluble form to a urea-insoluble form by transpeptidation beween a glutamine residue on one fibrin strand and a lysine e-amino residue on an adjacent fibrin strand. In general, when a pair of coagulation proteins interacts, one of them, the enzyme, converts the second from substrate to product; the substrate is often a proenzyme, and the product an enzyme, which then catalyzes yet another similar reaction. The probable exceptions to this rule are Factors VIII and V, which interact with phospholipid and another protein in a more complex manner.[11] Modern theory considers that prothrombin is activated Factor X (Xa). Factor X in turn can be activated by two independent pathways: one, the extrinsic pathway, involves tissue factor; the other, the intrinsic pathway, involves only blood constituents. Thrombin (Factor IIa) promotes the activation of two important factors, Factors V and VIII.[8] The addition of thromboplastin (Factor III) to the system will accelerate the coagulation (extrinsic coagulation). Factor VII is responsible for increasing the rate of action associated with tissue thromboplastin in the extrinsic system.[1]

When a person sustains a tissue injury, it is certain that extract of damaged tissue gains access to the blood and clotting could be promoted via the extrinsic system. The activation of the intrinsic pathway is more difficult to

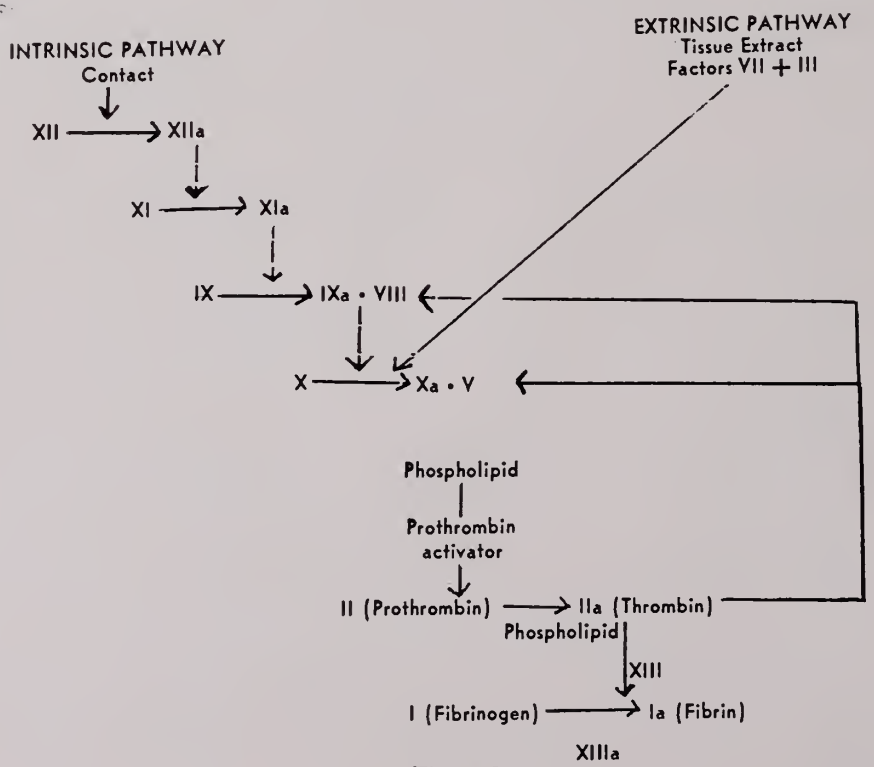


Figure 2

visualize. In the test tube it is "contact" with a foreign surface which activates clotting. Glass is itself an activating surface. Since most clotting experiments are carried out in glass tubes the intrinsic mechanism is activated in most test systems. The exact properties of the surface that promote clotting are not understood but some more coagulant and less coagulant surfaces have been defined. In general, most polymeric surfaces are less coagulant than glass. Factor XII is activated in some way by surfaces and is the initial factor in the intrinsic sequence. It is a sialoglycoprotein and is also known as the Hageman factor after the name of the person in whose blood it was first found to be lacking.[12]

Fibrin Formation

The formation of fibrin from fibrinogen is believed to occur in three steps. The proteolytic action of thrombin is responsible for the removal of four peptides from each fibrinogen molecule to form fibrin monomers. These monomers polymerize end to end and side to side to form a loose fibrin clot. The bonds between the fibrin molecules are then strengthened by the action of the fibrin stabilizing factor (Factor XIII) present in normal plasma.[1]

Waugh and Baughman[13] recently reported on a possible role of thrombin adsorption in relation to thrombus formation. In this study attention was directed to nucleation as the crucial event in thrombus formation. Adsorption of thrombin to nonpolar surfaces was studied using a clotting time assay procedure. In this study a thrombus model was described in which thrombin formed the anchoring layer for a thrombus; and thrombin, monomeric fibrin, and platelets were the constituents. Waugh and Baughman found an adsorption of 0.77 mg/M^2 at the solution-clean wall interface. Using a thrombin molecular weight of 33,600 and assuming a planar surface they calculated an adsorption of one thrombin molecule per 7900A^2, a minimum free energy of adsorption of −11.7 kcal/mole, an estimated thrombus adhesive strength of 10 kg/cm^2, and a thrombin-fibrin interaction free energy of —7 kcal/mole. In addition to the role of thrombin, fibrin and platelets in thrombus formation, it is also evident that several blood constituents (particularly members of the coagulation family) could be adsorbed and involved in nucleation; that the surface concentrations of these will be affected by the binding of nonnucleating constituents (possibly molecules such as serum albumin or globulin); and that the interaction sequences of nucleation and growth might be varied and complex.

Inhibition

A number of inhibitors of intrinsic blood coagulation have been studied in an effort to better understand the mechanism of interaction of various clotting factors. Pitlick et al. recently studied the role of heparin, heparin analogues, and hirudin.[14] These inhibitors primarily affect two clotting factors in the intrinsic scheme — Factor IXa and thrombin. They found that Factor IXa is sensitive to heparin and hirudin in plasma when coagulation is initiated by Factors XII or XI. Subsequent clotting factors remain inactive. Their studies with heparin and hirudin further clarified the role of thrombin in relation to Factors IXa and VIII. They concluded from their studies that Factor VIII readily reacts with Factor IXa and independently of thrombin when calcium ions and phospholipid are present.

Fibrinolysis

The uncontrolled formation of clots is believed to be regulated by intrinsic inhibitors

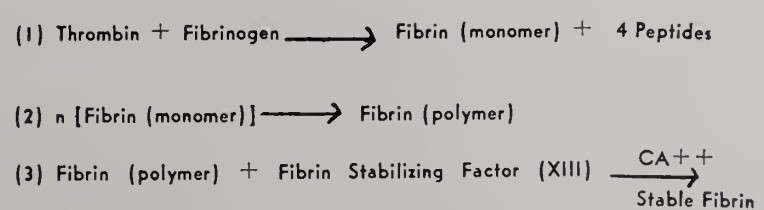


Figure 3

which prevent but do not block the reaction. An example of such inhibitory action is represented by the fibrinolytic system which has the ability to dissolve the fibrin clot. This clot dissolution is carried out by the action of the proteolytic enzyme plasmin, which occurs in plasma as the precursor plasminogen. The mechanism of the initiation of fibrinolysis is a complicated process (outlined briefly below) in which a proactivator system causes the activator system to convert plasminogen to plasmin.[1] Biggs[8] has stated that Factor XII activates the fibrinolytic system (Figure 4).

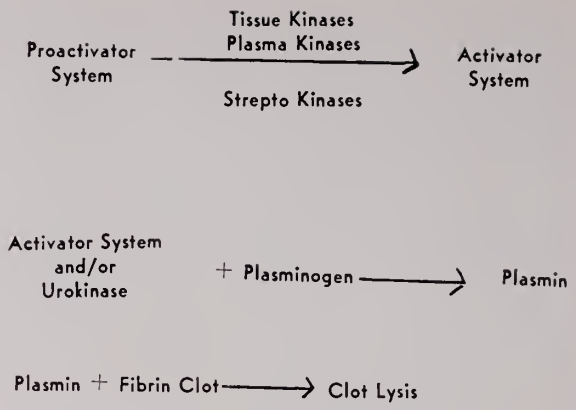


Figure 4

Summary

We have surveyed the most recent literature pertaining to the mechanism of blood coagulation. This discussion has been a necessary introduction to the next article where we will be concerned with the adsorption of the various clotting factors on surfaces and their interactions as proteins with surfaces.

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Finished

Once upon a time we used to read in the obituary column that "so-and-so completed his education, at such and such a college." But the phrase, I am glad to say, has about gone out of use. We now know that if a man's education is finished, he is finished.*

*M. Dale Baughman: Treasury of Stories.

To lengthen your life, shorten your meals.—Proverb.

Otolaryngology Clinics

Injuries to the Larynx and Trachea

Automobile Crash

DAVID J. BURAN, M.D.*

Too FREQUENTLY accident victims with respiratory distress are examined with no thought given to the possibility of laryngotracheal injury. Dangerous conditions may exist under minimally injured superficial neck structures. Severe fracture-dislocations of laryngeal cartilages and trachea with accompanying mucosal tears and hematomas, and even complete severance of the larynx or trachea can occur with no visual evidence of trauma or with only slight contusion or abrasion.

Often the patient is tracheotomized promptly, relieving respiratory distress but postponing the diagnosis of airway injury. Marked stenosis of the larynx and compromise of the voice can occur while the tracheotomy tube is in place; only with failure of detubation is the actual situation suspected and finally diagnosed. By this time the stenosis may be severe and the voice markedly compromised—making the long-term prognosis poor.

The majority of injuries of this type occur in auto crashes when the anterior neck strikes the upper rim of the steering wheel, crushing the larynx and trachea with the "hammer" action of the steering wheel against the fixed "anvil" of the cervical vertebrae. A slight reddening, swelling, or abrasion may be the only visual evidence of the injury. This same mechanism may occur as front seat passengers are thrown against the dash board or back seat passengers against the front seat.

It seems ironic that as the use of seat belts has increased, the number of head and neck injuries also has increased. However, many of those treated in emergency rooms would have been thrown from the car and killed had they not worn lap belts. Hopefully this trend can be reversed as more people are convinced of the value of regularly wearing shoulder-type belts.

Diagnosis

A minimum battery of diagnostic tests in suspected cases should include: (1) a complete head and neck examination with indirect laryngoscopy, (2) a chest x-ray, (3) a lateral x-ray of the larynx, (4) an x-ray of the cervical spine, (5) an esophagram, (6) an endoscopy. In some cases planograms of the larynx are helpful.

Management

If a tracheotomy was not done during the first phase of the injury a tracheotomy set should be at the bedside at all times and measures taken to prevent airway difficulties. These should include voice rest, bed rest, adequate moisturization of air, and the use of steroids.

As soon as the patient is able to tolerate a general anesthetic a direct lar-

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yngoscopy is performed, allowing thorough examination of the internal structures, to be followed by definitive repair of the injury through an anterior collar-line incision. A tracheotomy is necessary before major repairs of the damaged larynx are undertaken. Repair of disrupted mucosa and vocal cords and internal splinting of the larynx with a stent* precedes reduction of fractures with direct wiring where necessary. A variety of materials have been used for internal splints, including acrylic, silastic, and portex. Stents should be maintained in place for a minimum of six weeks with prophylactic antibiotic coverage. Efforts should be made to attain as good a voice as possible, but airway stenosis is the prime problem to be avoided.

Case Report

A 17-year-old girl was brought into the emergency room after being involved in a car accident. She had been riding in the middle of the front seat and was thrown against the dash board but not out of the car. No seat belts were available in the vehicle.

The initial examination in the emergency room revealed a lethargic girl who apparently had not lost consciousness. Blood pressure was 120/74 and pulse, 104. There was a one-cm. laceration of the forehead and some tenderness and swelling of the submandibular area. Talking appeared to be an effort and there was some inspiratory stridor but no air hunger. Palpation of the neck revealed crepitation lateral to the larynx bilaterally. The chest and abdomen appeared normal and the only other abnormalities were lacerations of the left knee and anterior calf.

Eight hours later the crepitation and tenderness in the neck had increased. The inspiratory stridor was unchanged and there was an expiratory "flutter." Her alertness had diminished and affectation was inappropriate. Neurological examination revealed no other pathologic signs.

At this point slight abrasions were noted on the anterior neck. Because her intracranial status was judged to be precarious, direct laryngoscopy was postponed. Air exchange was adequate and effortless; therefore no tracheotomy was performed but a tracheotomy set was kept in readiness at the bedside.

Within the next 24 hours her level of consciousness improved markedly but her voice became more hoarse and finally she could only whisper. Respirations continued effortless.

Three days after admission her intracranial status was stable enough to permit direct laryngoscopy, which showed disruption of mucosa and cartilages. A tracheotomy was performed. Exploration of the larynx was then performed through an anterior collar-line incision. The mucosa was repaired; an internal stent was placed, and the cartilages were reduced and wired directly.

The stent was retained without difficulty for two months. The mucosa was then found to be well healed with no granulations resulting. The airway proved to be adequate and detubation was no problem.

Initially, voice quality was a problem as she spoke only in a loud whisper. Voice quality continues to be a problem. She will be followed closely; injection of one vocal cord with teflon paste may be necessary in the future.

*See Test Your Word Score, page 973.

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He has been a doctor a year now and has had two patients—no, three, I think —yes, it was three; I attended their funerals.—Mark Twain

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Every man desires to live long, but no man would be old.—Jonathan Swift

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hyoscine hydrobromide	0.0065 mg.	0.0065 mg.	0.0195 mg.
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Alcoholism

Acute Alcoholic Withdrawal Syndrome

THOMAS R. MARVIN, M.D.*

THE CLINICAL COURSE of chronic alcoholism may periodically be interrupted by the acute alcohol withdrawal syndrome, which represents a serious medical condition. Symptoms usually appear within a few hours to a few days after cessation of a prolonged period of excessive drinking which may be as brief as a few days. The syndrome is characterized by marked variations in the severity and duration of symptoms not only from patient to patient but even in the same patient at various periods. Physicians inexperienced in the treatment of acute alcohol withdrawal states are prone to overtreat mild manifestations and undertreat severe manifestations. Based on our experiences with close to 9000 alcoholics over a period of several years we have developed a successful treatment program which to date has not resulted in any fatalities attributable directly to the acute withdrawal syndrome even among patients presenting with delirium tremens.

The Alcohol and Drug Addiction Unit of the Willmar State Hospital was organized to treat exclusively patients with problems of alcohol and drug addiction. During the five-year period from January 1964 through December 1968 we have cared for 9289 patients admitted to the service, of whom 96 percent were chronic alcoholics, although about 4 percent of these were also addicted to, or involved in the excessive use of non-narcotic drugs; less than 4 percent of the total admission represented pure narcotic or non-narcotic drug addiction. Ninety-eight percent of the chronic alcoholics showed definite symptoms of alcohol withdrawal states; among these about 4.8 percent were diagnosed as suffering from delirium tremens. Details of the patient population are presented in Table 1.

Of the more than 9000 subjects treated, 19 died following admission to the hospital and five of these deaths were a direct consequence of chronic alcoholism (Table 2). None of the patients with delirium tremens died and there were no suicides.

Our nearly 5 percent incidence of delirium tremens is consistent with that reported by Victor (1966) and Kaim et al. (1969). How-

TABLE 1

Causes of Admission to the "Alcohol and Drug Service" of the Willmar State Hospital During a Five-Year Period

	Number of Patients		
	Males	Females	Totals
Alcoholism	7,514	1,094	8,608
Alcoholism and Drug Addiction or Excessive Involvement*	177	169	346
Drug Addiction or Excessive Involvement*	26	77	103
Narcotic Addiction	164	68	232
		Total	9,289
Acute Alcohol Withdrawal States			7,740
Delirium Tremens (DT)			278 (4.8%)

*The drugs involved in descending order of frequency were: amphetamines, barbiturates, meprobamate, chlordiazepoxide; much less often they were: diazepam, glutethimide; dextropropoxyphene, ethchlorvynol, hallucinogens.

TABLE 2

Cause of Death Over a Five-Year Period Among 9,289 Patients with Problems of Alcohol and Drug Addiction

	Number of Patients
Myocardial Infarction	6
Cerebral Vascular Accident	3
Terminal Liver Diseases (Alcoholic)	3
Acute Hemorrhagic Pancreatitis (Alcoholic)	2
Acute Glomerulonephritis	2
Acute Pulmonary Edema	1
Bronchogenic Carcinoma with Brain Metastasis	1
Astrocytoma, Grade IV	1
Total	19

*Chief of Service, Alcohol and Drug Addiction Unit and Medico-Surgical Unit, Willmar State Hospital, Willmar, Minnesota.

ever, Victor notes that 15 percent of such cases end fatally. Others (Tavel, 1960) also reported approximately 15 percent deaths (39 of 289 alcoholics) associated with delirium tremens over an eight-year period, but noted that only 6 percent of these apparently resulted solely from delirium tremens in the absence of other lethal complications.

Symptoms of the Acute Alcohol Withdrawal Syndrome

The major manifestations of sudden partial or complete withdrawal of alcohol following a period of excessive drinking vary according to the severity of the withdrawal state. For a clearer understanding of the symptomatology and the principles of management it is helpful to divide the acute withdrawal syndrome into three main categories according to the intensity of the presenting symptoms (Table 3). These

TABLE 3
Symptoms of Acute Alcohol Withdrawal States

			"Severe"	
	"Mild"	"Moderate"	DT absent	DT present
Gastrointestinal				
Anorexia; Nausea	±	++	+++	+++
Diarrhea	—	—	±	±
Epigastric distress	±	++	+++	+++
Vomiting; Retching	—	—	±	±
Motor Disturbances				
Tremulousness	+	++	+++	+++
Incoordination	—	—	—	±
Sleep Disturbances				
Restless sleep; Insomnia	+	++	+++	+++
Nightmares	—	—	±	++
Vegetative Disturbances				
Tachycardia; Hyperpnea	—	—	+	+
Fever	—	—	±	±
Hyperhydrosis	+	++	+++	+++
Mental Disturbances				
Apprehension	++	+++	+++	+++
Agitation	—	—	+++	+++
Panic	—	—	—	±
Confusion	—	—	—	+
Disorientation	—	—	—	+
Sensorium	Clear	Clear	Clear	Clouded
Psychotic Manifestations				
Hallucinations	—	—	—	+
Delusions	—	—	—	+
Muttering delirium	—	—	—	+
Paranoid trends	—	—	—	±

may be characterized as 'mild,' 'moderate,' or 'severe,' with or without delirium tremens. In relation to another classification (Kissin and Gross, 1968) our 'severe' state without delirium tremens would apparently be equivalent to their 'impending delirium tremens.' Victor (1966), who has called attention to the dynamic nature of the relationship of the various alcohol withdrawal states in terms of progression of severity and their potential to merge into one another, believes that no available treatment effectively prevents delirium tremens or is capable of altering its duration or mortality rate. We, however, are inclined to agree with Kissin and Gross (1968) and others (Kaim, 1969) that with early recognition and vigorous treatment of the incipient phases of the disorder, the emergence of delirium tremens can be successfully forestalled.

Physical Examination X-ray and Laboratory Tests

Upon admission, all patients receive a complete physical examination, chest x-rays, and the following tests: urinalysis, CBC and hematocrit. Additional evaluation, when indicated, includes serum electrolytes, blood sugar, BUN, liver function tests, serum amylase, blood alcohol and x-rays of the head.

General Principles of Management of the Acute Alcoholic Withdrawal Syndrome

1. Hospitalization is imperative except for selected cases of mild withdrawal.
2. Early recognition and treatment of any coexisting disease and injuries.
3. Avoidance of isolation of the patient, darkness and physical restraint. Frequent reassurance particularly to patients with delirium tremens.
4. Frequent monitoring of vital signs.
5. Adequate rest, sedation and nourishment. Avoid feeding solids to heavily sedated patients. Over 90 percent of our patients with delirium tremens are fairly lucid mentally and are able to eat sufficiently within 12 hours after admission.
6. Correction of electrolyte and fluid imbalance and control of any intercurrent infection. We agree with Cohen (1963) that infection and/or electrolyte imbalance can precipitate borderline hepatic decompensation into hepatic coma.
7. Avoid intravenous fluids during early phases of alcohol withdrawal, as such patients are overhydrated. Diuretics are used when indicated (Knott and Beard).
8. Avoid, if possible, any physical restraint. Combative and disoriented patients are prone to become more so when restrained.

9. Avoid narcotics, psychic energizers, antidepressants and barbiturates. Antidepressants frequently cause severe agitation and confusion if administered during the withdrawal state.
10. PRN orders for sedatives may result in oversedation of some patients, precipitating respiratory failure and collapse, when any movement of the patient is interpreted by the nursing staff as hostility. PRN orders for sedatives should be tailored to control the patients' and not the nursing staff's apprehension and discomfort.
11. Persistent and unresponsive delirium tremens is a medical emergency—akin to acute coronary episodes, diabetic coma or thyroid storm—and requires constant nursing care. When delirium tremens lasts as long as three days, a search for specific cerebral, cardiac, pulmonary, hepatic, or renal complications is imperative.
12. Head injury, latent epilepsy or brain tumor should be looked for particularly in the alcoholic patient who is over 40 years of age and exhibits convulsions for the first time.
13. Recurrence or late occurrence of withdrawal seizures or withdrawal deliria may be caused by withdrawal from barbiturates or other drugs. Many patients while readily admitting a drinking problem may conceal their excessive involvement with tranquilizers and/or sedatives.
14. In cases of multiple addiction (alcohol plus tranquilizers such as chlordiazepoxide and diazepam) we have seen patients recover from their alcohol withdrawal syndrome in a few days only to go into a second withdrawal syndrome a few days later (usually about the ninth day following cessation of the use of the drug). This is manifested by agitation, tremulousness, confusion and paranoid trends. We refer to this state as chlordiazepoxide or diazepam withdrawal syndrome. It requires vigorous treatment, with gradual reduction of the dosage.
15. We believe that the alcoholic patient can be well managed in private hospital settings as well as in state hospitals and other treatment centers. If properly treated in such facilities he will not disturb other patients, frighten personnel or damage property.
16. Bland diet, antacids and supplemental feedings are used as indicated during the withdrawal state.
17. Although we have had no indications for tracheotomy in this series, we believe that this procedure should be performed, and performed early, when it is indicated.

Drug Therapy

As to pharmacological agents, we agree with Kaim (1968) that it is necessary to use drugs which are adequate pharmacological substitutes for alcohol. Barbiturates, chlordiazepoxide, meprobamate, paraldehyde, oxazepam, and diazepam belong in this category. The phenothiazines, which include two drugs frequently used for delirium tremens (chlorpromazine and promazine), exhibit a low degree of cross-dependence with alcohol. Accordingly, they do not specifically suppress the alcohol withdrawal syndrome. Details of drug regimens are given in Table 4.

Since the specific metabolic disturbances which follow the withdrawal of alcohol are not yet known, drug therapy must be largely empirical with the aim of achieving symptomatic

TABLE 4

Drug Treatment of Acute Alcohol Withdrawal States According to Symptom Severity

Medication	"Mild" Dose (mg)*	"Mild" Duration	"Moderate" Dose (mg)*	"Moderate" Duration	"Severe" Dose (mg)*	"Severe" Duration
1. DIAZEPAM	5 tid	1 or 2 days	10-20	Stat	20-30	Stat
					or	
			10 tid	1 or 2 days	20 i.m.	Stat
			5 tid	1 or 2 days	10-20 qid	1 day
			10 i.m. q 4 hrs	prn agitation	10 qid	2 days
					10 tid	1-2 days
					5 tid	1-3 days
					20 i.m. q 4 hrs	prn agitation
2. METHYPRYLON	300 hs	1 or 2 nights	300 hs†	2 or 3 nights	300 hs†	5-7 nights
or						
3. CHLORAL HYDRATE	1 Gm hs	1 or 2 nights	1 Gm hs†	2 or 3 nights	1 Gm hs†	5-7 nights
4. PROMETHAZINE After 2. or 3. is stopped.	50 hs	1 or 2 nights	50 hs	1 or 2 nights	50 hs	1 or 2 nights
5. PARALDEHYDE For agitation not controlled by diazepam.					15 cc q 4 hrs	12-24 hrs
6. CHLORPROMAZINE For combative patients only.	50 i.m.	Stat	50 i.m.	Stat	50 i.m.	Stat

*Administration per os except when otherwise specified.
†With repeat

control.

Fraser (1957) has suggested that drugs with sedative action are effective because they may be adequate pharmacologic substitutes for alcohol. Chlordiazepoxide, particularly, has been reported to be useful in preventing two most common and serious developments—convulsions and delirium tremens (Kaim et al., 1969), (Kissin and Gross, 1968). Kissin and Gross (1968) note that the increased anxiety of the alcoholic patient appears to contribute to primarily an organically based disruption, and reduction of anxiety would be anticipated to contribute to recovery. Others—Gross and Goodenough (1966) and Kaim (1969)—have suggested that disruption of sleep caused by alcohol and its subsequent withdrawal may also play a significant role in the etiology of the acute alcoholic psychosis. Rapid eye movement or dream sleep is reduced during the intoxication phase and is increased markedly during the withdrawal phase. In addition, profound disturbances of delta or deep stages of sleep have been noted. It is suggested that chlordiazepoxide, unlike other sedatives including barbiturates, does not suppress rapid eye movement activity, but reduces anxiety sufficiently to allow the patient to sleep despite the intense dream-nightmare activity. We believe that diazepam has a similar pharmacological action.

We have found diazepam to be an excellent therapeutic agent in the treatment of 'mild' and 'moderate' withdrawal syndrome and in many patients with the 'severe' category. It has been used routinely in the treatment of withdrawal syndrome in 3463 patients in this series. The drug has a good tranquilizing effect without inducing lethargy. (This treatment makes possible early ambulation and self-care.) It also has a beneficial effect on the tremor. It can be used even when the patient still has alcohol in his system without potentiating excitement and confusion. We have observed no respiratory depression, and even in large doses the incidence of ataxia is comparatively low. The drug apparently has no adverse effects on the liver and, in our experience, does not depress the blood pressure.

Diazepam, which is known to be an effective anticonvulsant in status epilepticus, has been effective in practically 100 percent of the patients in this series in preventing withdrawal seizures and obviating the necessity of recourse to anticonvulsants, such as diphenylhydantoin.

Any and all drugs used in the management of the alcohol withdrawal state have some disadvantages. Barbiturates frequently cause excitement and additional confusion if the patient still has alcohol in his system. Phenothiazines, such as chlorpromazine and promazine, appear to exhibit a low degree of cross-dependence with alcohol and do not specifically suppress the acute symptoms. Moreover, phenothiazines may aggravate or cause seizures (Benor and Ditman, 1966) or hypotensive reactions (Chafetz, 1967). According to Knott et al. (1967), chloral hydrate may often cause deep and unexpected depression in a patient with alcohol still present in body fluids. In our experience, all sedatives, particularly barbiturates, frequently cause agitation, confusion and occasionally respiratory depression if alcohol is still present in the body fluids.

For the extremely belligerent and combative patient who is still intoxicated and unmanageable, we administer a single 50-mg dose of chlorpromazine intramuscularly, which usually produces sleep lasting for three or four hours. We have seen no respiratory depression from the potentiating effects of this combination (chlorpromazine and alcohol) in this dosage.

Paraldehyde also has its disadvantages (Hoagland, 1966; Smith, 1968). We have found it to be a fairly safe short-acting sedative; we do not use this agent, however, when the patient still has alcohol in his system. In adequate dosage, paraldehyde will control agitation in severe delirium tremens and frequently produce sleep when nothing else seems to work. It is administered in 1½ oz of fruit juice. We advise against the use of paraldehyde parenterally because of the danger of pulmonary edema when given by these routes.

Broad-spectrum antibiotics are given prophylactically for severe withdrawal with delirium tremens. Also, during severe withdrawal, we administer large doses of thiamine and B complex daily intramuscularly, and multivitamins plus additional thiamine, ascorbic acid and niacin orally.

Since alcoholics are dependency-prone par excellence, extreme caution is advised in the use of tranquilizing and sedative agents after termination of the withdrawal period.

Summary

The acute alcohol withdrawal syndrome, a serious medical condition, may be divided into three main categories: 'mild,' 'moderate,' or 'severe,' with or without delirium tremens. A practical therapeutic regimen for each category is described, including considerations of general principles of hospital and nursing care. Drug therapy is centered on the use of diazepam orally or parenterally to achieve symptomatic control, and chloral hydrate or methyprylon for nighttime hypnotic. Paraldehyde is administered to some subjects when diazepam fails to control agitation. Chlorpromazine, usually a single intramuscular dose, is used for extreme belligerence and/or combativeness in the acutely intoxicated patient. It is felt that the alcoholic patient can be adequately managed in private hospital settings.

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Samuel F. Haines, M.D.

The cover is a painting of a farm in Fillmore County near a cottage owned by me. When I painted it, the farm was owned by "Shorty" Cambern and was worked by him. I liked it because it was a good example of a working farm with a minimum of "modern" improvements. I also liked "Shorty," and any time I could spend there was a "special occasion."

I am retired from active practice and am a member of the emeritus staff of the Mayo Clinic. I still live in Rochester, Minnesota, and spend my summers in Massachusetts on the shore. I am a member of the American Artists Professional League but am not good enough to be. I have fun painting, but I could not make a living at it. I am pleased that you are to use my painting on your September issue.

Owl

A wise old owl lived in an oak,
The more he saw, the less he spoke;
The less he spoke, the more he heard;
Why can't we all be like that bird?—Anon.

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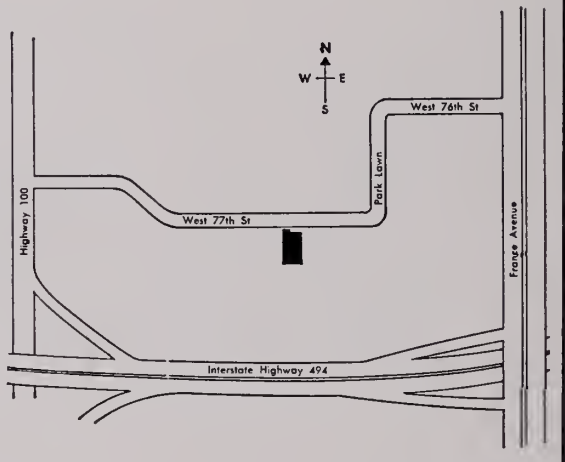
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Case Report

Studies on X-Chromosome Aneuploidy at the Faribault State School

HEINZ H. BRUHL, M.D., FREDERICK D. PEAGLER, D.D.S., M.S.
and ROBERT J. GORLIN, D.D.S., M.S.

OVER THE PAST five years several studies have been carried out at the Faribault State Hospital which have been concerned with various aspects of X-chromosome aneuploidy. Peagler[1] attempted to evaluate the relationship of clinical appearance and age on the observed frequency of sex chromatin masses in epithelial cells of the buccal mucosa.

Alter et al.[2] investigated the same screened population, describing the dermatoglyphics* in the XXYY syndrome and noted a low mean total ridge count, an increased frequency of unusual hypothenar ridge configuration, wide *atd* angle, distal axial triradius, ulnar displaced proximal triradii, and simian lines.

The purpose of this paper is to present the clinical findings of five males with X-chromosome aneuploidy isolated from 2,297 adults housed at the Faribault State Hospital.

Methods

Buccal smears were obtained on 1,214 adult males, from which a group of 10 chromatin-positive individuals were identified, karyotyped, and thoroughly examined. This included total skeleton roentgenographic survey, lateral head plates including mandible and complete dental films, upper and lower dental casts, and color-blind tests. A 24-hour sample of urine was collected and finger and palm prints were obtained for dermatoglyphic analysis.

Buccal smears of 1,083 adult females yielded two individuals who had two Barr bodies per nucleus and two who were chromatin-negative.

Karyotype Analysis

Karyotype analysis of the males yielded the following: XXY—five cases; XXYY—four cases; XXXY—one case. Karyotype analysis of the adult females proved two to be XXX and the other two to have XO Turner's syndrome. The females are for the moment not pertinent to this study.

The clinical description will be limited to the patients with XXYY (Cases 1-4) and XXXY (Case 5) Klinefelter's syndrome.†

Case Reports

Case 1

Twenty-eight-year-old male, 72 inches tall, with normal phallus, small firm testes and marked gynecomastia. Beard light and limited to chin. Normal pubic hair, but scanty axillary and no chest hair. Facial acne evident. Tendon reflexes hypoactive. Horizontal nystagmus present. Intelligence quotient—57. History of sexual aggression against younger sister.

Case 2

Twenty-five-year-old male, 72 inches tall, with small penis and atrophic testes. Breasts not enlarged. Facial, axillary and chest hair absent; female pubic escutcheon. Tremors of hands and tongue. Tendon reflexes hypoactive. High pitched voice. Intelligence quotient—52 to 69. History of convulsions in early childhood and of sexual assault of an 11-year-old girl.

Case 3

Twenty-two-year-old male, 71 inches tall. Normal penis, atrophic testes. No gynecomastia. Facial and body hair distribution normal. Lumbar lordosis, pes planus evident. Conjugate gaze and convergence impaired. Intelligence quotient—53. History of sexual deviation, masturbation in public, sodomy, indecent assault on a four-year-old girl.

Case 4

Thirty-two-year-old negro male, with lumbar lordosis, right hemiparesis, right hemiatrophy and G. M. seizures. Height 66.5 inches. Marked varicose ulcers. Normal male genitalia, no gynecomastia. Beard normal, but body hair scanty. Intelligence quotient—38. History of birth injury, aggressive and assaultive behavior, and sex play with other boys.

Case 5

Twenty-five-year-old white male, 72 inches tall, with a high boyish voice. Thin with long lanky limbs; hips with a female flare. Absence of beard and chest hair; good

*See Test Your Word Score, page 973.
†See Klinefelter's Syndrome, page 820 of the July Issue.

axillary and pubic hair of masculine type. Mild gynecomastia. Normal phallus, but testicular atrophy. Dermatoglyphics: low ridge count and high frequency of arches. I.Q.—39 to 42. Behavior: friendly. Excessive masturbation, even in public, and sex play with other boys.

Results

Estimations of urinary gonadotrophic levels performed on the XXY, XXYY and XXXY patients ranged from 80 m.u. to 200 m.u. (normal 5-50 m.u. per 24 hours). X-ray studies of the entire skeleton did not show any significant abnormalities. Tests for color blindness were negative in all 10 male patients. The ages of the mothers, at the time of birth of eight males, ranged from 22 to 34 years; one mother was 48 years old, and the age of one was unknown.

The I.Q.s for the different types of Klinefelter's are given in the Table. The I.Q. range for the men with XXYY karyotype is above 50; the others are below. The low I.Q.s of Case 5 in the XXY group and of Case 4 in the XXYY group are explained by the fact that these two men had suffered a superimposed organic brain damage at the time of birth as indicated by history, early seizures, and spastic quadriplegia in one case, and hemiplegia and hemiatrophy in the other.

TABLE
I. Q. and Maternal Age on Klinefelter's Syndrome

	I. Q.	Maternal Age At Patient's Birth
XXY		
1. J. M.	37–42	22 yrs.
2. E. R.	38–50	Unknown
3. R. S.	40–45	48 yrs.
4. D. K.	35–40	22 yrs.
5. S. T.	10–16	25 yrs.
XXYY		
1. L. D.	51–64	22 yrs.
2. D. K.	52–69	34 yrs.
3. G. L.	52–69	30½ yrs.
4. D. P.	38	29 yrs.
XXXY		
C. E.	42	24 yrs.

Discussion

The incidence of chromatin-positive males was approximately as expected, i.e., about one percent of institutionalized males. The maternal age factor, so important for the meiotic nondisjunction in Down's syndrome, is less striking in Klinefelter's syndrome. It has been postulated that each additional X-chromosome in the male further depresses the intelligence; but the addition of one Y-chromosome appears to counteract this effect. Peterson and Gorlin[3] examined the patients from this population with XXYY syndrome and noted a high incidence of varicose veins and varicose dermatitis.

The incidence of XXX females (two per 1,100) was lower than that observed in several other studies (average: one per 250 institutionalized females). Conversely, the occurrence of two patients with Turner's syndrome among 1,100 females was higher than expected (one per 2,500 institutionalized females).

Summary

A study of 2,297 adults (1,214 males, 1,083 females) at Faribault State Hospital revealed 10 chromatin-positive males. Karyotyping this group yielded five XXYs, four XXYYs, and one XXXY. Two females were found with two Barr bodies per cell (XXX), and two were noted to have XO chromatin-negative Turner's syndrome. The age of the mothers and the intelligence level of the patients with Klinefelter's syndrome seemed to have no correlative significance.

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As a nation we've been going soft; well on our way to becoming a country of beauty-rested sissies. How many of us can run around the block without puffing? How many of us can work a full, hard day without using up our last ounce of energy? We've long prided ourselves on our comfortable life. Perhaps it has been too comfortable.*

*Victor G. Heiser, R.N., A Journal for Nurses.

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See Clinical Considerations section on last page...

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Urinary Tract Infections (due to susceptible strains of gram-negative bacteria)†	0.8-1.2 mg./kg. for 7-10 days	Larger doses or additional antibacterial therapy should be considered in severe urinary tract infections or in resistant cases involving the renal parenchyma or anatomic anomaly.	up to 5 mg./kg.
Other Infections including bacteremia, infected surgical wounds, severe soft tissue infections, and respiratory tract infections (due to susceptible strains of gram-negative bacteria)	3 mg./kg. for 7-10 days		

†Alkalinization of the urine may be a useful therapeutic adjunct.

Patients with Impaired Renal Function
To minimize the risk of ototoxicity in patients with impaired kidney function, only the first dose should be that normally recommended. Each subsequent dose should be half or less of that recommended for patients with normal renal function, depending upon the degree of renal impairment.

In patients with renal failure who are undergoing 14-hour hemodialysis twice weekly, administration of 1 mg./kg. GARAMYCIN Injectable at the end of each dialysis period has been suggested.

Clinical Considerations
Indications: GARAMYCIN Injectable is clinically effective in infections due to susceptible strains of gram-negative bacteria, including *Pseudomonas aeruginosa,* and species of indole-positive and indole-negative *Proteus, Escherichia coli,* and *Klebsiella-Aerobacter.* Bacteriologic studies should be conducted to identify the causative organism and to determine its sensitivity to gentamicin sulfate. Sensitivity discs of the drug are available for this purpose. If the susceptibility tests indicate that the causative organism is resistant to gentamicin sulfate, other appropriate antibiotic therapy should be instituted.

IN VITRO INHIBITION OF CLINICALLY IMPORTANT BACTERIA BY GENTAMICIN SULFATE (TUBE DILUTION STUDIES)

BACTERIA	No. of Strains Tested	No. of Strains (%) Inhibited by: 4 mcg./cc. or less		8 mcg./cc. or less*		No. of *In Vitro* Studies
Staphylococcus aureus	1,210	1,200	(99%)	1,206	(99%)	11
Pseudomonas aeruginosa	885	771	(87%)	828	(93%)	16
Escherichia coli	836	736	(88%)	779	(93%)	11
Indole-positive and indole-negative *Proteus* species	477	210	(44%)	358	(75%)	12
Klebsiella-Aerobacter species	292	205	(70%)	231	(79%)	10

*Number of strains (%) of gram-negative bacteria inhibited by 10 mcg./cc. or less are as follows: *Pseudomonas aeruginosa,* 828 (93%); *Escherichia coli,* 792 (95%); *Proteus* species, 393 (82%); *Klebsiella-Aerobacter* species, 284 (97%). From same studies as above.
Source: Package Insert

This drug should be limited to the treatment of serious infections caused by gram-negative bacteria, particularly *Pseudomonas aeruginosa, Proteus* and other susceptible organisms, with due regard for relative antibiotic toxicity. Therefore, the drug should be considered for use against gram-negative: 1. Bacteremia; 2. Infected surgical wounds; 3. Severe soft tissue infections, including burns complicated by sepsis; 4. Respiratory tract infections; and 5. Selected cases of urinary tract infection.

Contraindications: GARAMYCIN Injectable is contraindicated in individuals with a history of hypersensitivity or toxic reactions to gentamicin.

Warnings: Patients receiving treatment with GARAMYCIN should be under close clinical observation because of the toxicity associated with the use of this drug. Ototoxicity, vestibular and auditory, can occur in patients, primarily those with pre-existing renal damage, treated with GARAMYCIN Injectable, usually for longer periods or with higher doses than recommended.

GARAMYCIN Injectable is potentially nephrotoxic, and this should be kept in mind when it is used in patients with pre-existing renal impairment. Kidney function diminished by infection of the upper urinary tract may, however, improve during effective treatment with GARAMYCIN Injectable.

Concurrent administration of potentially ototoxic drugs such as streptomycin and kanamycin or of potentially nephrotoxic drugs such as polymyxin, colistin, and kanamycin with gentamicin sulfate has not been shown to afford any clinical advantages and, moreover may result in additive toxicity. Monitoring of vestibular, cochlear, and renal function will provide guidance for therapy in such cases.

Precautions: In patients with impaired renal function in whom serious infection develops, serum concentrations of the drug may rise, with consequently increased risk of ototoxicity. In these patients or in those in whom recommended dosage or duration of therapy must be exceeded as a life-saving measure, routine studies of kidney function should be performed when possible. These may be supplemented by evaluation of the vestibular and auditory function and measurement of serum concentration of the drug when feasible. Serum concentrations of gentamicin should be maintained below the range of 10-12 mcg./ml. to reduce risk of ototoxicity.

Ordinarily, treatment should not be given for more than 7 to 10 days or be repeated unless required for serious infection not responsive to other agents.

As with other antibiotics, treatment with GARAMYCIN Injectable may occasionally result in overgrowth of nonsensitive organisms. If superinfection occurs, appropriate therapy is indicated.

Safety for use in pregnancy or the potential for fetal ototoxicity or nephrotoxicity have not been established. Studies in pregnant animals have not revealed teratogenic or ototoxic effects in the fetus. GARAMYCIN Injectable should not be used in pregnant patients or in women of childbearing age unless its use is deemed advisable by the physician.

Adverse Reactions: The overall incidence of ototoxicity considered related to treatment with GARAMYCIN Injectable was 2.8 per cent (16 of 565 patients). Contributory factors (two or more factors were relevant to most patients) were as follows: 10 had azotemia, 10 received a total of 1 gram or more of the drug, 7 had recently received other potentially ototoxic antibiotics (streptomycin or kanamycin), and 5 were over 60 years of age. Six also had decreased high-tone hearing acuity, which returned to or toward normal in the 4 patients retested.

Analysis of BUN data indicated that 4 (2%) of 172 patients showed increases in BUN that were probably related to treatment with GARAMYCIN Injectable. Of 20 increases probably or possibly related to treatment, 7 were reversible, 9 occurred in terminal patients, and 4 had no follow-up.

Other adverse reactions associated with treatment were one instance each of urticaria, decreased hematocrit, and reversible depression of granulocytes with normal bone marrow. Other rarely reported and possibly treatment-related adverse reactions were anemia, increased reticulocyte count, rash, purpura, drug fever, hypotension, convulsions, twitching, salivation, nausea, vomiting, increased transaminase activity (SGOT or SGPT), increased serum bilirubin, decreased serum calcium, and joint pain.

Packaging: GARAMYCIN Injectable, 40 mg./cc., 2-cc. multiple-dose vials, for intramuscular administration.

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AHFS CATEGORY 8:12.28 S-029

Neurological Grand Rounds

Vascular Disease of the Spinal Cord

ERNESTO INFANTE, M.D. and MILTON ALTER, M.D., Ph.D.*

KNOWLEDGE ABOUT the vascular pathology of the spinal cord remains meager despite recent advances in diagnostic techniques. There are several reasons for this: the spinal cord is perhaps less carefully studied during routine postmortem examinations, the main arteries in the spinal cord are almost never investigated, and it is very difficult to apply the available radiological contrast techniques to spinal vessels because of their small caliber and inaccessibility.

Toward the turn of the century cases of spinal cord softenings secondary to vascular disturbances began to appear in the literature with increasing frequency. This change in opinion spread to the English-speaking countries where Bastian, at the time a consultant of the University College Hospital, became its most outspoken defender. Bastian said: "By many writers and practitioners the term 'myelitis' is used in a somewhat vague manner, and with an evident tendency to include under it as many different diseases of the spinal cord as possible." He intimated that in the great majority of "acute myelitis" cases the affection is caused not by an inflammation, but by thrombosis of some of the vessels of the spinal cord.

Recent publications have contradicted the report of Blackwood (1958) who found only 11 cases from 1909 to 1958 among 3,737 postmortems at the National Hospital in London. However, Blackwood accepted the possibility that more cases might have been missed "because of the nervous system failing to be fully examined."

Vascular Supply of the Spinal Cord

Until late in the nineteenth century the vascular supply of the cord was thought to be purely segmental. Adamkiewicz (1882), studying 29 human spinal cords, proved that only a few radicular arteries contributed to the irrigation of the cord: that the arteries were not equal to the number of nerve roots, as was previously believed. This "reduction" in the number of segmental, radicular arteries takes place in the embryo between the sixth week to the fourth month of prenatal life, during which time the arrangement is changed from a purely segmental pattern to that of an adult. The irrigation of the anterior and the posterior aspects of the cord are different.

Anteriorly

The anterior spinal artery and the anterior radicular arteries supply the anterior part of the cord. They reach the anterior medial fissure of the cord where they divide into ascending and descending branches, anastomosing with each other and thus forming a continuous arterial channel all along the cord. Their regional distribution is as follows:

*Chief, Neurology Service, Minneapolis Veterans Hospital.

Cervical-thoracic Region

This extends caudally to T3-4. Down to C4, the irrigation is supplied by the anterior spinal artery, a branch of both vertebral arteries.

Caudal to C4, two to three radicular arteries provide the blood supply which reaches the midline alternately from the right or the left sides. The most constantly occurring arteries are the ones which follow the C6 cervical nerve and first thoracic (T1). They are branches of the ascending cervical and superior intercostal (from the cervico-intercostal trunk) respectively.

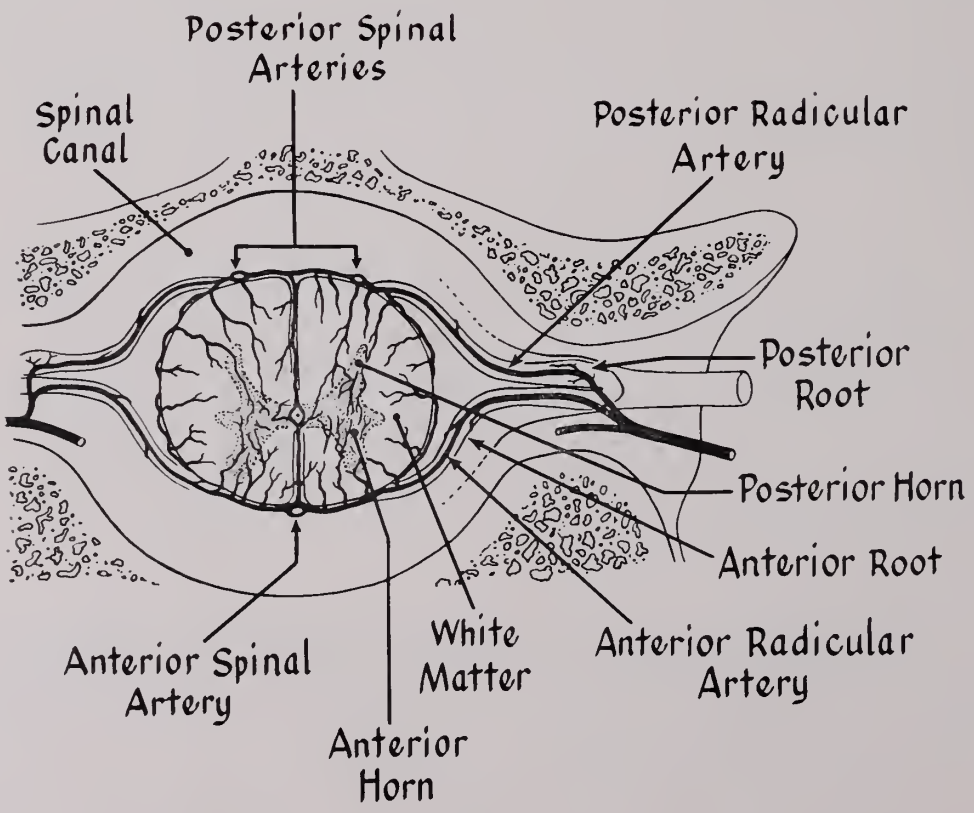
Mid-thoracic Region

This comprises four to eight thoracic segments. Here the vascularization is poor, but a fair-sized radicular artery is usually present at T5.

Thoracolumbar Region

This has a very rich vascularization which includes the largest of all radicular arteries—the "arteria radicularis magna of Adamkiewicz." This artery is a branch of either one of the last intercostal arteries or of the first lumbar arteries with origin in the thoraco-abdominal aorta. It may reach the cord anywhere between T8 and L2. According to Corbin, in 80% of cases it accompanies one of the T8-12 roots on the left side. In this case, it is the only vascular supply for this area. In the other cases, when its origin is lumbar, there is usually another artery at a root from T7-9.

In either case, the descending branch of Adamkiewicz's artery reaches the medullary canal where it forms a loop and thus anastomoses with the two posterior spinal arteries. Occasionally, another radicular artery may reach



Figure

the cord at the lower lumbar region.

Posteriorly

The upper cervical area is supplied by the two posterior spinal arteries, branches of the vertebral arteries. These run along the posterior lateral sulcus all along the cord, being reinforced by approximately 20 posterior radicular arteries, smaller in number than the anterior counterparts and reaching the cord at variable levels. These arteries form numerous anastomoses with each other, constituting a plexus rather than a longitudinal channel.

Laterally

The anterior and posterior arterial trunks described above give rise to numerous small vessels which anastomose on the outer surface of the spinal cord. They form the so-called arterial corona. A cross-section of the cord reveals the intrinsic blood supply of the cord.

Intrinsically:

The Sulcal Arteries

These are branches of the anterior spinal trunk and penetrate the median sulcus irrigating the right and left sides in an alternating fashion. The number is approximately 200, with the poorest share going to the thoracic region.

They irrigate the *gray substance* including the anterior horns, the periependymal gray, the base of the posterior horns and Clarke's column. In the *white matter* they irrigate the anterior column (pyramidal tract), the deep portion of the lateral pyramidal and spino-thalamic tracts, and the deep portion of the posterior columns. Roughly, the anterior supply feeds two thirds of the cord. A larger part of the total transverse of the area in the cervical and lumbosacral cord than the thoracic cord is supplied from anterior vessels.

Peripheral Arteries

These are branches of the vasa corona and posterior spinal arteries. They irrigate the posterior one third of the cord including the white and the gray matter of the posterior horns.

There are proven anastomoses between the different intra-medullary arteries. However, the functional value of the anastomoses has not been proven. Thus, spinal cord vessels can be considered "terminal arteries."

Venous Supply

Segmental veins leave the midline of the cord anteriorly and posteriorly. These join in a venous plexus which surrounds the cord and finally drain into six to eight radicular vessels which leave the spinal canal along the nerve roots.

Physiopathology

Ischemic pathology of the cord can result from either a global deficit of blood supply or the obstruction of an important medullary vessel. During hypotensive episodes, areas of the cord farthest away from the main arterial trunks are the ones most in danger of infarction. These are the "border zones" between two main vascular territories: T3 or T4 and L1 or L2 longitudinally and the border zone between the anterior and posterior spinal arteries transversely, the "juxta-ependymal" area, according to Zülch. If the vascular defi-

cit involves only one vessel, the area of infarction will be limited to that irrigated by the involved vessel unless good anastomoses exist, which is usually not the case. Thus, obstruction of one of the juxta-medullary vessels would result in a *segmental infarct,* and obstruction of one of the larger extramedullary vessels will cause a pluri-segmental infarction.

Cord Infarction

Ischemic infarction of the cord is usually of acute onset. However, in unusual cases there can be some prodromol manifestations which are called *tranantericur ischemic attacks of the cord.* The latter are characterized clinically by sensory symptoms of radicular pain usually involving several segments, by dysesthesia* or by transient motor deficits.

Dejerine in 1906 was the first to describe this entity. He called it "intermittent claudication of the cord" and presented three cases of middle-aged patients who complained of dysesthesia, cramps and paresis of one or both lower extremities after exercise. These would disappear with rest after about five minutes and invariably recur with exercise. At rest, no abnormal findings could be elicited, but with exercise, disturbances in the motor and sensory modalities could be found. Sometimes the only positive sign was a Babinski response. This has been referred to by Gotthard and Soderbergh as "an afternoon Babinski phenomenon."

Arterial pulses were normal in these cases. Dejerine thought that in all of his cases the etiology was probably luetic, but post-mortem proof was lacking. Since Dejerine's original description, more cases have been described. Severe atheromatous involvement of the vascular supply to the cord with obstruction of the abdominal aorta or the lumbar vessels has usually been found. Intermittent claudication of the cauda equina by an herniated disc may simulate true claudication secondary to arterial obstruction of the Charcot type (Table 1).

Recently Cossa has presented seven cases in which the symptomatology has been secondary to the involvement of the large Adamkiewicz artery by atheromatous obstruction, compression by a disc or a meningioma. He has labelled these "syndrome of the arteria radicularis magna."

All have been older patients, ranging from 51 to 72 years of age. In these cases, there was no correlation of symptoms with exercise. The symptoms were usually of sudden onset, clearing after a few days and recurring at a

*See Test Your Word Score, page 973.

TABLE I

	TYPE	Pain	Site	Sensation	Muscle
A	Intermittent Claudication of the Cauda Equina	Paresthesia	Definite "march" of symptoms along the lower limb	On examination sensory changes in lumbar and sacral dermatomes	Wasting
B	Intermittent Claudication Secondary to Arterial Obstruction of Charcot	Severe "gripping" pain	In various sites simultaneously	No deficit	or hypotonia
C	Dejerine's intermittent Claudication of the Spinal Cord	Symptoms may be similar to "A" but on examination there is evidence of upper motor neuron involvement.			

later date. All of his patients had marked spasticity, clonus, and sensory and sphincteric disturbance. The period of transient deficit may last from a few days to several months before a completed, irreversible infarction takes place.

Cord infarction is usually of sudden onset, occurring at night or during the morning upon arising. The patient complains of sudden, excruciating radicular pain immediately followed by paralysis and sphincter disturbances. One may differentiate several syndromes depending on the part of the cord involved.

Anterior Spinal Artery Syndrome

The anterior spinal artery syndrome was first described by Preobajensky (1904), who believed it was caused by syphilitic obstruction of the anterior spinal artery. Patients have sudden onset of pain, corresponding to the level of the lesion, followed by paraplegia below the lesion, initially flaccid, and becoming spastic after a few days. Sensory changes include a dissociated sensory loss below the level of the lesion, pain and temperature being abolished with preservation of vibratory and position sense. Initially, during the period of "spinal shock," there are sphincter disturbances consisting of fecal and urinary retention. Trophic changes may develop later.

Primary thrombosis of the anterior spinal artery was first reported by A. Van Wierinjen (1968). Previously, all recognized cases of obstruction were secondary to embolism. The occlusion must occur at the level of the anterior radicular arteries or in the main vascular trunks where they originate. The following conditions have been implicated at post-mortem examination: syphilitic arteritis, atheroma, subluxation of a cervical vertebra, diabetes and spondylosis. Coarctation and occlusion of the aorta have also been antecedent causes of cord infarction.

Posterior Spinal Artery Syndrome

The posterior spinal artery syndrome was first described by Williams in 1895. It is a very rare condition. The clinical picture includes radicular pain at the level of the lesion, abolition of deep sensation below the level of the lesion, and paresthesias. There is anesthesia at the level of the lesion only. Reflexes are absent below the lesion. Sphincters are rarely involved. At times mild pyramidal signs below the level of the lesion are seen. All cases of obstruction of posterior spinal arteries have been attributable to emboli.

Sulcal Artery Syndrome

The sulcal artery syndrome is mentioned in the literature, although a pathologically documented report is lacking. Regional muscle weakness secondary to anterior horn cell involvement or a Brown-Sequard-like picture may be seen.

Transverse Lesion

Transverse cord lesions are seen after involvement of one of the radicular arteries by different etiological factors and at times by obstruction at their origin (aortic aneurysm or atheroma). A reduction in blood flow in several radicular arteries simultaneously, as seen in dissecting aneurysm of the aorta or in cases of hypertension, produces an infarcted area involving those border zones where the irrigation is more precarious; e.g., T4, L1-2, or occasionally

C3 in the longitudinal plane or the central part of the cord and periependymal area in the transverse plane. The extent of the infarcted area varies, depending on the acuteness and severity of the episode, the state of the vessels in that particular patient, etc. Clinically these patients have the usual findings seen in transverse cord lesions with a variable degree of severity.

Chronic Ischemia

More and more cases of chronic ischemia of the cord are being described in the literature. Neumayer and Jellinger, in 1962, described 21 cases with this disorder which had a picture-like amyotrophic lateral sclerosis. The patients had slowly progressive, distal muscle atrophy of ascending character initially involving the lower extremities in 10 patients and the uppers in six. A combination of upper and lower motor neuron involvement was found, including fasciculations. No sensory deficits were elicited. Electromyography in four cases showed findings typical of anterior horn cell involvement.

The mean age of the group was 65 years and the duration of illness was about four years. Only one patient had bulbar findings. Autopsy showed diffuse, severe atherosclerosis of the abdominal and thoracic aorta and symmetrical cavitation and necrosis of the anterior horn. The pyramidal tract was involved predominantly over the upper thoracic area.

The pathogenesis of chronic cord ischemia is postulated to be a generalized deficit of irrigation which selectively involves those areas that are most sensitive to anoxia. This mechanism was experimentally proven by Krogh who progressively clamped the aorta in animals and produced damage to the anterior horns and pyramidal tracts.

Similar syndromes of chronic ischemia were described by Skinhoj and by Pierre Marie and Foix (trephomalacie anterievre). In these cases the small muscles of the hands were involved. Thus, a clinical picture resembling motor neuron disease might be caused by cord malacia.

TABLE 2

Etiological Factors in Cord Ischemia.

I. Causing a circulatory deficit at the perimedullary level:
   1. Diseases of the Arteries
      a. Atherosclerosis
      b. Lues
      c. Polyarteritis nodosa
   2. Emboli

II. Causing a circulatory deficit at a distance:
   1. Large Vessel Obstruction
      a. Aortic atherosclerosis
      b. Dissecting aortic aneurysm
      c. Thrombosis of one of the subclavicular arteries
   2. Congenital Aortic Malformation
   3. Complication of Surgical Procedures
      a. On the aorta
      b. Thoracic surgery
         —Sympathectomy
         —Pneumonectomy
         —Thoracoplasty
      c. Abdominal aortography
      d. Local anaesthesia
   4. Cord Compression by
      a. Tumors
      b. Arthrosis
      c. Disc herniation
      d. Trauma

The Etiology of Spinal Cord Ischemia

The most common etiologies are listed in Table 2.

Aortic Surgery

Adams, in 1956, reported 24 cases of cord ischemia associated with aortic surgery. In 11, an aortic coartation was corrected; in seven, the aorta was resected; and in six, there was temporary occlusion of the aorta. He concluded: (1) Surgery to the aorta below the kidneys is rarely complicated by cord damage because this part of the aorta contributes little blood supply to the cord. (2) Above the kidneys, occlusion of the aorta below the subclavian artery and ligature of the lower thoraco-intercostal vessels were found to cause cord damage. The latter may have resulted from occlusion of a low thoracic arteria radicularis magna.

In spite of hypothermia or shunt procedures, when the lower intercostals are occluded, cord damage supervenes because of inadequate collateral circulation.

The safe time for occlusion of the circulation is probably under 18 minutes.

Cervical Spondylosis

At operations for cervical myelopathy, the cervical cord is seldom found to be compressed. In more than half of these cases, the neurological level of dysfunction does not correspond to the level of the bony lesions seen on x-ray films. The explanation is that the myelopathy is secondary to vascular compression. Only one to three anterior radicular and about three to five posterior radicular arteries irrigate the cord between C3-4 and T4-5. Therefore, when an important radicular artery at this level is compressed or occluded by the encroachment of an osteophyte on the corresponding arterial foramen or by thickened fibrous tissue surrounding the nerve roots, a myelopathy occurs which extends from about C4 to T1. Therefore, in corrective surgery of these processes, a laminectomy should always be combined with a decompression of the cervical nerve root.

Embolization

Embolic infarction of the cord is rare. This is due to the organization of the arterial supply to the cord which consists of vessels of small lumen originating by branching at right angles from the aorta, an orientation which does not make embolization easy. However, the apparent rarity of this entity could be due to the lack of a thorough examination of the spinal cord vessels at autopsy. The embolic material can be blood clots from valvular cardiac lesions from a myocardial infarction or from bacterial endocarditis. Tumors, parasites, gas, atheromatous material, fibrocartilaginous material and the nucleus pulposus may also embolize to the spinal cord.

Although Wolman maintains that chronic myelopathy is possible following repeated embolization with atheromatous material, a sudden onset is more typical.

Hemorrhage of the Spinal Cord

Hematomyelia has assumed decreased importance in the last few years as other types of vascular cord pathology have been recognized. In hemorrhage following cord trauma, Zülch and others demonstrated that ischemic necrosis results, due to arterial vasoconstriction following traumatic concussion of

the cord. Later, bleeding into the area occurs. The necrosis is central in the juxta-ependymal area which is most sensitive to anoxia: the "border zone" of Zülch. Spontaneous hematomyelia is usually secondary to vascular malformations.

Vascular Malformation of the Cord

The total number of cases of vascular malformation of the cord reported until 1930 was only 34. In recent years Arseni (1959) classified them as angioectasies, venous and arterial; they are characterized by linear or ampullar dilatation of a single vessel. The angiomata are classified as venous, arterial or arteriovenous; they consist of a conglomeration of tortuous vessels and are most often located in the lower thoracic area below T8. About 70 percent of the patients are males. The age varies from 21 months to 62 years.

Symptoms consist of subarachnoid hemorrhage in 25 percent of the cases and in 40 percent of the patients below the age of 14 years. This might be the only symptom in 50 percent of the cases; therefore, one should always think of this possibility in every case of subarachnoid hemorrhage in a young patient with negative cerebral angiography.

Signs of spinal cord involvement occur sooner or later in all cases, characterized by radicular pain and long tract signs in more than half the patients. Typically, the evolution is that of recurrent episodes of bleeding with involvement at the same cord level.

The diagnosis can be made with spinal x-rays and laminograms, but 78 percent of the cases are negative. Spinal fluid is abnormal in 80 percent of the cases with hemorrhages. The myelogram is positive in 50 to 85 percent of cases depending on the authors, the characteristic finding being the "corkscrew," "vermiform" appearance first described by Guillain and Alajouanine (1925). Selective spinal cord arteriography is often helpful. Selective injection of the different intercostal and lumbar arteries should be used for the malformations below the cervical thoracic junction. For cervical angiomas, brachial, subclavicular and vertebral injections are necessary. Djindjian described a total of 30 cases of cord hemagiomas, 13 of which were resected totally and two subtotally, all of them located below the T8 level. The malformations were small in size and fed by a single artery in most cases. Unfortunately, the high thoracic or cervical lesions are less accessible because of their size, complexity, and both anterior and posterior vascularization. Only palliative surgery can be done on the latter cases; but thanks to newly developed techniques, the treatment of these entities is now much brighter than it was a few years ago.

The cord may be involved not only by hemorrhage or by compression, as has been reported in the past, but by "stealing" of blood by the malformation and by subsequent ischemic necrosis as shown in case reports of Houdart, Djindjian and Hurth. A previously nonfilling arteria magna filled with blood following the surgical excision.

Subacute Necrotic Myelitis

This entity was first described by Foix and Alajouanine in 1926, and has ever since caused confusion and controversy. In their original publication they described an entity characterized clinically by a progressive, ascending paraplegia, initially of a spastic character and later becoming flaccid; a sensory disturbance, initially characterized by disassociation of sensation and later becoming global, also of ascending character; and albumino-cytological disso-

ciation in the cerebrospinal fluid. The course was subacute with death occurring in one to two years.

Anatomically, a necrotic myelitis originating at the lumbosacral level and extending into the mid-thoracic level is seen. Over this area there is a remarkable endomesovasculitis involving both the intra- and the extra-medullary vessels, which are considerably hypertrophied and dilated six to ten times their normal diameter.

The etiology was considered to be infectious; however, many authors have considered this entity solely a venous angioma with complications (Wyburn-Mason). Recent reports are increasingly in support of this view. Anthony, in 1962, reported five cases of combined vascular malformation with myelomalacia. He found leptomeningeal and perivascular changes and thick-walled veins, changes identical to the ones described by Foix and Alajouanine. Thus the syndrome could be caused by an arteriovenous angioma complicated by thrombophlebitis and other inflammatory changes.

Summary

Compared to cerebrovascular disease, the incidence of vascular involvement of the spinal cord has been considered negligible in the past. The growing number of cases reported in the literature during recent years casts some doubt upon the accuracy of this formerly accepted belief.

A brief review of the vascularization of the spinal cord, its more common clinical syndromes and their etiopathogenesis has been presented. With the application of improved techniques of arteriography in studies of the spinal cord and with more careful survey of the vascular supply during routine postmortem examinations, further clarification of the etiopathogenesis of many as yet obscure myelopathies will be achieved.

If references are desired, please contact the author.

Freud and Psychiatry

With the advent of psychiatry, medicine got back to the fundamentals with which it began, such as demons which were in the mind and couldn't be cut out with a knife or cured with a pill. Psychiatry affected not only medicine but the national economy, the makers of couches and notebooks having to work overtime to supply the sudden need.

According to Freud, the psyche is made up of three parts, the id, the superego, and the ego. The id is the naughty part, lurking in the shadows of the subconscious and thinking up devilish things to do. The superego, which acts like a spoilsport big brother, is always repressing the id and kicking it around, though occasionally the id sneaks by it and causes trouble. As for the ego, it tries to get the superego and the id to be friends, but becomes terribly discouraged.*

*Richard Armour: It All Started with Hippocrates, 1966.

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PSYCHIATRIC RESIDENCIES: We offer nothing but excellent psychiatric training in a stimulating, well-organized program located in a culturally advantaged community. Approved psychiatric training. Traverse City State Hospital, Michigan Department of Mental Health. Three and five year programs. Salary, three year program: $11,359; $11,922; $12,925. Five year program: $12,945; $14,950; $17,393; $23,198; $24,409. NIMH-GP Stipends available. Located in Michigan's serene, scenic recreation area on Grand Traverse Bay. Contact Dr. Paul E. Kauffman, Director of Training, Traverse City State Hospital, Traverse City, Michigan 49684. An equal opportunity employer.

LOCUM TENENS WANTED: G.P. for summer months or any portion thereof. Clinic serving population area of 12,000. City has new hospital, new clinic building; new swimming pool; metropolitan city near. Write or call Warren Clinic, Warren, Minn. 56762. 742-6231, area code 218.

TEN MAN MULTISPECIALTY group needs an ophthalmologist and another pediatrician. New clinic building, complete laboratory and x-ray facilities. 180 bed modern hospital across street from clinic. Early share-holder status. Salary open. Write or call the Lenont-Peterson Clinic, Ltd., C. A. Tietz, M.D., area code 218, 741-4292, Virginia, Minnesota 55792.

MT. TELEMARK, Cable, Wisconsin, 4.5 acre wooded hill overlooking Mt. Telemark. Beautiful site for ski cabin. $5,000.00 Telephone 612-927-9490.

BUILDING SUITED FOR 10 Doctor Clinic. Located in Columbia Hts. N.E. Central Avenue, Minneapolis. Steel and concrete building containing 18,500 sq. feet and parking area 17,105 sq. ft. Priced right. 29% down. Contract for deed or own financing. Contact N. Segal, 544-1768 Minneapolis or Calhoun Realty Co., 2939 Hennepin Avenue, Minneapolis.

(Continued to page 1024)

The girth control pill



Tepanil® Ten-tab

(continuous release form)

(diethylpropion hydrochloride)

works on the appetite not on the 'nerves'

When girth gets out of control, TEPANIL can provide sound support for the weight control program you recommend. TEPANIL reduces the appetite—patients enjoy food but eat less. Weight loss is significant—gradual—yet there is a relatively low incidence of CNS stimulation.

Controindicotions: Concurrently with MAO inhibitors, in patients hypersensitive to this drug; in emotionally unstoble patients susceptible to drug abuse.

Worning: Although generolly safer than the omphetamines, use with great coution in patients with severe hypertension or severe cardiovasculor disease. Do not use during first trimester of pregnoncy unless potential benefits outweigh potential risks.

Adverse Reoctions: Rarely severe enough to require discontinuotion of therapy, unpleosant symptoms with diethylpropion hydrochloride hove been reported to occur in relotively low incidence. As is chorocteristic of sympothomimetic ogents, it may occosionolly couse CNS effects such os insomnio, nervousness, dizziness, onxiety, and jitteriness. In contrast, CNS depression has been reported. In o few epileptics an increose in convulsive episodes has been reported. Sympathomimetic cardiovascular effects reported include ones such os tochycordio, precordiol poin, orrhythmio, polpitotion, ond increosed blood pressure. One published report described T-wave changes in the ECG of a healthy young male after ingestion of diethylpropion hydrochloride; this was on isoloted experience, which hos not been reported by athers. Allergic phenamena reported include such conditions as rosh, urticorio, ecchymosis, ond erythemo. Gastrointestinal effects such os diorrheo, constipation, nausea, vomiting, and abdominal discomfort hove been reported. Specific reports on the hematopoietic system include twa each of bone marrow depression, ogranulocytosis, and leukopenia. A voriety of miscellaneous odverse reoctions have been reported by physicions. These include complaints such as dry mouth, headoche, dyspneo, menstrual upset, hoir loss, muscle poin, decreased libido, dysuria, and polyuria.

Convenience of two dosoge forms: TEPANIL Ten-tab toblets: One 75 mg. tablet doily, swallowed whale, in midmorning (10 a.m.); TEPANIL: One 25 mg. toblet three times doily, one hour before meals. If desired, an oddltional tablet moy be given in midevening to overcome night hunger. Use in children under 12 yeors of oge is not recommended.

T-006A / 1/70 / U.S. PATENT NO. 3,001,910

THE NATIONAL DRUG COMPANY
DIVISION OF RICHARDSON-MERRELL INC.
PHILADELPHIA, PENNSYLVANIA 19144



Painful night leg cramps...

unwelcome bedfellow for any patient– including those with arthritis, diabetes or PVD

One thing patients can sleep without, particularly patients with chronic disease conditions such as arthritis, diabetes or PVD, is painful night leg cramps. Although seldom the presenting complaint, night leg cramps can tie your patients up in painful knots. Now, just one tablet of QUINAMM at bedtime can usually bring an end to shattered sleep and needless suffering. Your patients will sleep restfully—gratefully—with QUINAMM, specific therapy to prevent painful night leg cramps.

Prescribing Information—Composition: Each white, beveled, compressed tablet contains: Quinine sulfate, 260 mg., Aminophylline, 195 mg. **Indications:** For the prevention and treatment of nocturnal and recumbency leg muscle cramps, including those associated with arthritis, diabetes, varicose veins, thrombophlebitis, arteriosclerosis and static foot deformities. **Contraindications:** QUINAMM is contraindicated in pregnancy because of its quinine content. **Precautions/Adverse Reactions:** Aminophylline may produce intestinal cramps in some instances, and quinine may produce symptoms of cinchonism, such as tinnitus, dizziness, and gastrointestinal disturbance. Discontinue use if ringing in the ears, deafness, skin rash, or visual disturbances occur. **Dosage:** One tablet upon retiring. Where necessary, dosage may be increased to one tablet following the evening meal and one tablet upon retiring. **Supplied:** Bottles of 100 and 500 tablets.

THE NATIONAL DRUG COMPANY
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PHILADELPHIA, PENNSYLVANIA 19144

Quinamm™
(quinine sulfate 260 mg., aminophylline 195 mg.)

Specific therapy for night leg cramps

0915A 1/70

Advance

Omnipen (Ampicillin) for Prophylaxis

Prior to Oral Surgery

D. D. BENSON, D.D.S.*; D. E. WAITE, D.D.S.†;
W. H. HALL, M.D.‡; and G. W. CARROLL, D.D.S.#

POSTOPERATIVE BACTERIAL invasion of the blood following surgical procedures is well documented.[1,2,3,4] Previous studies have reported the results of prevention of bacteremia after oral surgery. Efficacy of phenoxymethyl penicillin (penicillin V), erythromycin, cloxacillin and lincomycin in prevention of bacteremia has also been reported.[5,6,7,8,9,10] The purpose of this study was to evaluate the effectiveness of ampicillin under similar conditions. When taken orally, it is well absorbed and was therefore administered per os in this study.

Materials and Results

Criteria for patient selection were entirely dependent on the need for oral surgical procedure. Generally, patients had depleted dentitions requiring multiple extractions, alveoplasty, tori removal, impacted tooth removal, etc. Ampicillin in capsule form (500 mg) was given every six hours in four successive doses beginning 24 hours before surgery. Blood for aerobic and anaerobic cultures was drawn immediately after surgery and again 18 hours later. Twenty-five patients were examined: none of them with pre-existing infection or valvular heart disease and none who had been taking antibiotics. None of the patients had positive cultures.

Comment

The results of this study indicate that administration of ampicillin prior to oral surgery procedures is satisfactory prophylactic therapy for prevention of postoperative bacteremia. Surgical procedures varied from simple extraction to extensive multiple tooth removal and alveoplasty. Since all cultures were negative, a relationship between type of procedure and bacteremia could not be established.

Ampicillin has been shown to be effective against gram-positive organisms, usually considered susceptible to penicillin G, phenethicillin and penicillin V and also against a variety of gram-negative organisms. Like penicillin, ampicillin is also destroyed by penicillinase. Our data would indicate it to be satisfactory prophylaxis in prevention of bacteremia, although careful follow-up of patients with suspected heart valve damage is imperative. Symptoms of postoperative bacteremia or subacute bacterial endocarditis require immediate patient re-evaluation. It is important to note that ampicillin is a semi-synthetic penicillin derived from a basic penicillin nucleus; therefore patients giving a history of allergy to a penicillin should not be given the antibiotic. In our study there were no untoward reactions.

Summary

Omnipen (ampicillin) was given orally, 500 mg every six hours, as a prophylactic regimen prior to oral surgical procedures in 25 patients. Blood cultures obtained immediately after operation and 18 hours later were negative in every instance. Ampicillin appears to be an effective antibiotic in the attempted prophylaxis of bacterial invasion of the blood stream following oral surgery.

*Oral Surgery Resident, University of Minnesota, Minneapolis.
†Professor and Chairman, Division of Oral Surgery, School of Dentistry, Minneapolis.
‡Chief of Medical Service, Veterans Administration Hospital, Minneapolis.
#Chief, Dental Service, Veterans Administration Hospital, Minneapolis.
References may be secured from the author or the reprints.

Classified Advertisements

(Continued from page 1020)

TROUT STREAM FRONTAGE on Cascade River. Also Forest and Meadow Cabin Sites. N. Shore, in Forest, 2 mi. to Pike L. boat launch area, 3 mi. to Lake Superior, 10 mi. to town, Cook City. Airport N. of town. Long term lease. E. HARVEY, Grand Marais, Minn. 55604.

WANTED: Two General Practitioners, or specialists willing to combine specialty with general practice for active and progressive community located in north-central Minnesota in the heart of rich dairy land. Easy access to Twin Cities via Interstate 94, excellent school system within community, colleges nearby. Excellent recreational area with many lakes nearby for year 'round sport activity. Modern hospital & C & NC unit in community. Good guarantee or partnership arrangement. Possibility of new medical clinic upon guarantee of serving community. Write MINNESOTA MEDICINE — 449, 375 Jackson St., St. Paul 55101.

OB-GYN WANTED for 25 man multi-specialty group with corporate benefits. Newly remodeled and expanded facilities close to well-equipped, well-staffed 180 bed hospital. Competitive salary and early shareholder status. Recreation area. Write or call East Rrange Clinics, Ltd., O. P. Friedlieb, M.D., (218) 741-0150, Virginia, Minn. 55792.

TWO MAN group in St. Paul area is desirous of week end coverage. If interested, all Robert L. Powers, M.D., 488-6777.

ADAMS CLINIC, P. A., a long established medical group in Hibbing in Northern Minnesota offers excellent income, profit sharing retirement benefits, life and health insurance, a new building only two blocks from a modern well staffed hospital in an atmosphere free from pollution and strife. The Clinic wishes to add a Board Certified or Board Eligible Surgeon, Orthopedic Surgeon, Internist, and General Practitioner. The community has a drawing area technical school, a junior college and recreational opportunities in all directions. An ideal place to raise a family. Only three hour drive to Twin Cities. Will pay expenses for an interview. Phone—(218) 262-3425.

INTERNIST AND GENERAL PRACTITIONER wanted to join a five-man clinic group in Minneapolis. Complete laboratory and X-ray with board roentgenologist. Excellent hospital staff associations. Salary arrangement to start with, early partnership. Write MINNESOTA MEDICINE—289; 375 Jackson, St. Paul 55101.

EDUCATION PLUS: What midwestern high school of 170 boys currently has alumni at Harvard, Princeton, Swarthmore, M.I.T., McGill, London and Oxford (Rhodes Scholar), welcomes Americans, and produces great hockey teams? St. Johns-Ravenscourt School, Winnipeg 19, Manitoba. Headmaster: H. John P. Schaffter, M.A. (Cambridge), 204-453-3016.

DESIROUS OF OBTAINING qualified physicians for a four man group in the fields of internal medicine, surgery, OB-GYN, General Practice. Please call me collect at 715-386-2311 at any time so I may offer you further details. M. A. Cornwall, M.D., Hudson, Clinic, 226 Locust Street, Hudson, Wisconsin 54016.

WANTED: General Practitioner or Internist, to join four man group in St. Paul. Partnership possible in one year. Dr. V. L. Sommerdorf, 1239 Payne Avenue, St. Paul, Minnesota 55101. Call: (612) 771-5577.

GENERAL PRACTITIONER wanted to join well-established practitioner. New clinic building—90 miles east of St. Paul—city of 14,000. Early partnership with full hospital facilities. Ideal location. L. W. Picotte, M.D., Chippewa Falls, Wisconsin.

EMERGENCY ROOM PHYSICIAN: Our medical staff has authorized the establishment of a medical organization to provide coverage for the hospital emergency room. Such an organization is now being planned. We are seeking a fulltime physician to assist in the development of and to direct the new organization. Remuneration open. Write: Emergency Room Committee, Unity Hospital, 550 Osborne Road, Fridley, Minnesota, 55432 or call: Administrator—612-786-2200.

PART TIME, set your own hours, in either downtown Mpls. or downtown St. Paul doing physicals mainly on executive and professional men. $17.50 per hour. Write: MINNESOTA MEDICINE—47, 375 Jackson, St. Paul 55101.

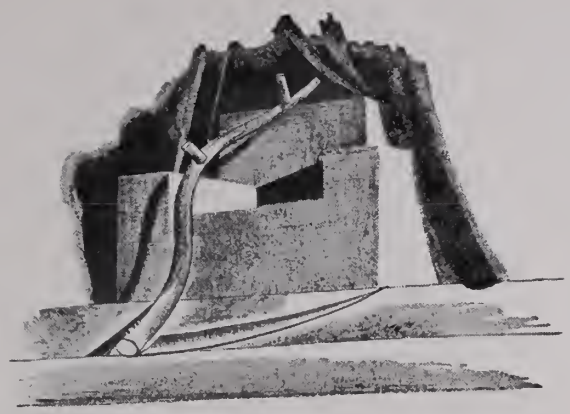
NEW EXPANDING OPPORTUNITIES for family physicians and physicians specializing in pediatrics, internal medicine, urology, anesthesiology; in medically-awakening community. Contemporary, automated, 105-bed, new hospital to be completed in the fall of 1970. Present hospital to be converted into long-term unit. Patient service area 50,000 people. Medical staff leading and supporting recruitment efforts. Excellent community location, forty miles equi-distant to Milwaukee or Madison. Complete educational, cultural and recreational facilities. A new medical-dental building and 130-bed skilled care nursing home being constructed adjacent to the new hospital ready for occupancy January, 1971. Immediate satisfaction in practice, income and family living. Special assistance if needed. Write or call Paul R. Glunz, M.D., Watertown Memorial Hospital, 1301 E. Main Street, Watertown, Wisconsin 53094; telephone 414-261-4210 for more information.

WANTED: General practitioners, Internist, Pediatrician, Orthopedic Surgeon, Obstetrician and Gynecologist for the Bemidji Clinic of Bemidji, Minnesota. Outdoor sports advantage second to none. The Bemidji Clinic now consists of three general practitioners, one internist, two general surgeons, one obstetrician, one otolaryngologist, and one ophthalmologist. If interested contact Duane E. Carlson, Business Manager, Bemidji Clinic, Bemidji, Minnesota.

WANTED: Physician for emergency room work to begin September 1, 1970. Needs Minnesota license, annual salary $25,000. Average work week 30 hours. Contact Thomas W. Votel, M.D., 612-488-6777, St. Paul, Minnesota.

WANTED: Part-time Minnesota-licensed physician to help cover in Extended Care Facility, over 200 beds, mostly geriatrics. Phasing out tb. unit. Working hours and compensation negotiable. Contact Administrator, Nopeming Sanatorium, Nopeming, Minnesota, Tel. 624-5725.

WANTED: Internist to join 4 internists in Minneapolis, Minn. Active referral practice. Group closely affiliated with University of Minnesota and maintains clinical teaching appointments. Starting salary $26,000.00. Full partnership in 3 years. Write: MINNESOTA MEDICINE 451, 375 Jackson, St. Paul 55101.



In Memoriam

A great man who neither sought nor shunned greatness, who found glory only because glory lay in the plain path of duty.—Macaulay

EDWARD A. REGNIER, M.D.

Dr. Edward A. Regnier, 75, a Minneapolis surgeon for 50 years, died June 11. He was former chief of staff at St. Mary's and Abbott Hospitals and also was on the staff of Hennepin County General Hospital.

Dr Regnier received his medical degree from the University of Minnesota and was clinical associate professor emeritus at the University since 1962.

He was a past president of the Minneapolis Surgical Society and the Minnesota Academy of Medicine; a member of the American Medical Association and Hennepin County Medical Society, and a Life Member of the Minnesota State Medical Association.

Dr. Regnier is survived by his wife, a daughter and three sons.

JAMES B. CAREY, JR., M.D.

Dr. James B. Carey, 45, a member of the University of Minnesota faculty, died March 3rd. A graduate of the University of Minnesota Medical School, Dr. Carey had been a clinical fellow of the American Cancer Society at the University.

He was a member of the Hennepin County Medical Society, American Medical Association, Minnesota State Medical Association, Minneapolis Society of Internal Medicine, American Gastroenterological Association, American Society for Clinical Investigation, Central Society for Clinical Research and the Association of American Physicians.

Dr. Carey is survived by his two daughters.

VICTOR R. KRUEGER, M.D.

Dr. Victor R. Krueger, 56, tuberculosis specialist in Nopeming, died July 1. Dr. Krueger had served on the staff of the Nopeming Sanatorium since 1940. Most recently he had been the associate medical director of the sanatorium and was director of the unit's outpatient department.

A graduate of the University of Wisconsin Medical School, he was a member of the American Medical Association, the Minnesota State Medical Association, the St. Louis County Medical Society and the American and Minnesota Thoracic Societies.

He is survived by his wife and a daughter.

ROBERT B. J. SCHOCH, M.D.

Dr. Robert B. J. Schoch, former chief health officer for St. Paul, died July 3, at the age of 86. A graduate of Northwestern University Medical School, he practiced in St. Paul from 1909 until 1934 when he began his city health service career.

He was a former president of the Ramsey County Medical Society, an honorary member of the directors of St. Luke's Hospital, a member of the American Medical Association and a 50 Club and Life Member of the Minnesota State Medical Association.

Dr. Schoch is survived by his wife.

WAYNE C. RYDBURG, M.D.

Dr. Wayne C. Rydburg, 67, Minneapolis general practitioner, died July 14. He had practiced in Brooten and Minneapolis. A University of Minnesota Medical School graduate, Dr. Rydburg was a staff member and former chief of staff at Swedish and St. Barnabas Hospitals.

Dr. Rydburg was a member of the Hennepin County Medical Society, the Minnesota State Medical Association and the American Medical Association.

He is survived by his wife, a son and two daughters.

CHARLOTTE J. MORRISON, M.D.

Dr. Charlotte J. Morrison, 60, Minneapolis pediatrician, died June 12. A graduate of the University of Minnesota Medical School, Dr. Morrison was a member of the Hennepin County Medical Society, the American Medical Association and the Minnesota State Medical Association.

She is survived by her two brothers, Dr. W. F. Morrison of Missoula, Montana and Dr. A. E. Morrison of Seattle, Washington.

JOHN V. FARKAS, M.D.

Dr. John V. Farkas, 57, St. Paul surgeon, died July 12. He received his medical education at the University of Minnesota Medical School and was a member of the Ramsey County Medical Society, the Minnesota State Medical Association and the American Medical Association.

Dr. Farkas is survived by his wife, two sons and a daughter.

WILLIAM J. MARTIN, M.D.

Dr. William J. Martin, chairman of the Division of Infectious Diseases and Internal Medicine of the Mayo Clinic, Rochester, and professor of clinical medicine, died suddenly, May 19, in Doctors' Hospital, Milwaukee.

He had received his Doctor of Medicine cum laude in 1943 from Georgetown University, where his rank was first in the class. He served an internship at the Georgetown University Hospital and was a fellow in medicine at Georgetown University.

After serving in the Medical Corps of the Army, Dr. Martin came to Rochester, Minnesota, in 1949, as a fellow in medicine, and in 1969 he was appointed to professor of clinical medicine.

Dr. Martin was a fellow of the American College of Physicians and a member of the American Medical Association, the American Association for the Advancement of Science, the Minnesota Society of Internal Medicine, the New York Academy of Sciences, the Minnesota State Medical Association, the Alumni Association of the Mayo Graduate School of Medicine and the Zumbro Valley Medical Society. He was also an associate editor of MINNESOTA MEDICINE.

His wife, a son and two daughters survive him.

THEO. P. E. GROSCHUPF, M.D.

Dr. T. P. Groschupf, 72, Bemidji, pediatrician, died April 23, in Douglas, Arizona. A graduate of the University of Minnesota Medical School, Dr. Groschupf began his practice in Bemidji in 1947. He together with Doctors D. D. Whitemore and D. F. McCann started the Bemidji Clinic.

Dr. Groschupf was a member of the American Academy of General Practice, the American Medical Association and the Headwaters Medical Society; and a Life Member of the Minnesota State Medical Association.

He is survived by three sons, one of whom is Dr. Richard Groschupf of Douglas, Arizona.

JAMES PARKER MAHLE, M.D.

Dr. James P. Mahle, 47, Minneapolis physician, died February 6. A graduate of the University of Minnesota Medical School, Dr. Mahle specialized in obstetrics and gynecology.

He was a member of the American Medical Association, the Minnesota State Medical Association and the Hennepin County Medical Society.

Dr. Mahle is survived by four children.

RICHARD M. HEWITT, M.D.

Dr. Richard M. Hewitt, 78, former consultant in the Section of Publications of the Mayo Clinic and a former associate professor of medical literature in the Mayo Foundation, died June 4.

He had been assistant editor of the Journal of the American Medical Association for three years and had received the George Washington University Alumni Achievement Award in 1944 for conspicuous achievement in medical journalism and the Distinguished Service Award of the American Medical Writers' Association in 1954. Also, he was a member of the Zumbro Valley Medical Society, an Associate Member of the American Medical Association and an Affiliate Member of the Minnesota State Medical Association.

The Old-Time Family Doctor*

Oh, where is the doctor who treated our ills
With Jalap and Rhubarb and Senna and squills
A much-whispered man—with the shaggy eyebrows
Who didn't know all of the "whys" and the "hows."

But had much common sense and a heart that was big
He rode on a horse or sometimes in a gig.
They say he has gone—has gone far, far away
And some folks are telling he's gone there to stay.

His place has been taken by one who's so smart
That he knows everything—but he hasn't the heart
Of the Old Family Doctor whom we used to know
So long and so well—and whom we loved so,
Who was kind and jolly—who'd laugh when we'd cry,
The Old Family Doctor—my best friend—Goodby.

*Spencer Michael Free (1856-1938), author of some five hundred poems, practiced medicine for almost fifty years in DuBois, Pennsylvania, and specialized in general surgery during his later years.



Remember how great milk of magnesia tasted?

Almost as good as castor oil.
But now you can spare the taste buds and spoil the patient with a modern Dulcolax tablet or suppository.

And Dulcolax works so predictably that the time of bowel movement can often be predicted. Tablets taken at night usually produce a bowel movement the following morning. Suppositories generally work in 15 minutes to an hour.

For preoperative preparation, a combination of tablets at night and a suppository the next morning usually cleans the bowel thoroughly.

Dulcolax suppositories may be particularly helpful when straining should be avoided, as in postoperative care. Keep in mind, however, that the drug is contraindicated in the acute surgical abdomen.

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"What she really needs, Doctor, is a shot of penicillin."

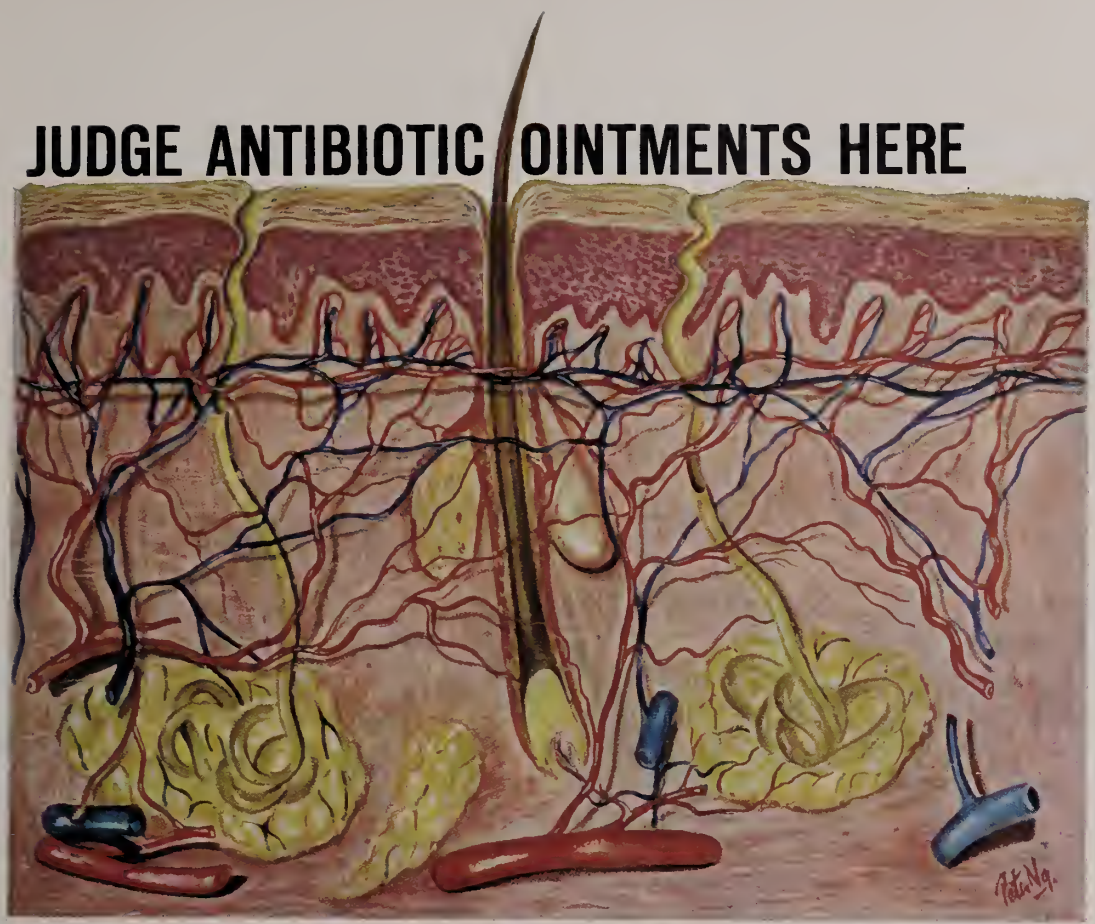
Maybe. Maybe not. In any case she needs something to control her sneezing, watery eyes and runny nose. And for most children over six, Novahistine® LP can be depended on to provide fast relief from summer colds and allergy. These continuous-release tablets have a vasoconstrictor-antihistamine formulation that begins working in minutes, then continues to provide relief for hours. A single Novahistine LP tablet, morning and evening, can keep most young patients free of symptoms all day and all night. Use with caution in individuals with severe hypertension, diabetes mellitus, hyperthyroidism or urinary retention. Caution ambulatory patients that drowsiness may result.

Novahistine® LP decongestant

(Each tablet contains 25 mg. of phenylephrine hydrochloride and 4 mg. of chlorpheniramine maleate.)

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Results on skin are final proof of any topical antibiotic's effectiveness

No in vitro test can duplicate a clinical situation on living skin. 'Neosporin' (polymyxin B—bacitracin—neomycin) Ointment has consistently proven its effectiveness in thousands of cases of bacterial skin infection. The spectra of the three antibiotics overlap in such a way as to provide bactericidal action against most pathogenic bacteria likely to be found topically. Diffusion of the antibiotics from the special petrolatum base is rapid since they are insoluble in the petrolatum, but readily soluble in tissue fluids. The Ointment is bland and nonirritating.

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Contraindications: This product is contraindicated in those individuals who have shown hypersensitivity to any of its components.

Supplied: Tubes of 1 oz., ½ oz. with applicator tip, and ⅛ oz. with ophthalmic tip.

Complete literature available on request from Professional Services Dept. PML.

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Clinical Extension of a pure Smooth Muscle Relaxant

TROCINATE®

Brand THIPHENAMIL HCl

400 mg./100 mg. S/C tablets

Trocinate relaxes all smooth muscles. Its direct action (musculotropic) does not involve the autonomic nervous system and it is not mydriatic. It is metabolized by the body and eliminated in the urine as harmless degradation products. Trocinate has a remarkable history of freedom from side-effects.

When a pure direct-acting smooth muscle relaxant is indicated, Trocinate is the drug of choice.

DIARRHEA (functional) . . . *the first 400 mg. tablet usually relieves the discomfort of diarrhea so promptly that it ceases to be a bother.*

DIVERTICULITIS—MUCOUS COLITIS . . . *the accompanying discomforts can be relieved by this direct smooth muscle relaxant.*

BLADDER SPASM . . . *relaxation is immediate. One or two tablets condition the bladder for cystoscopy in one hour.*

SPASTIC URETER . . . *the specific relaxing effect of Trocinate on the spastic ureter has been proven by animal studies and affirmed clinically. (J. Urol. 73:487-93)*

PRESCRIBING INFORMATION

WARNING: Do not give in advanced kidney or liver disease. PRECAUTIONS: Trocinate relaxes all smooth muscles. Large dosage or prolonged usage may cause feeling of weakness or can theoretically precipitate gall-bladder colic, due to relaxing the vascular and duct systems. Caution should be observed in patients with urinary bladder obstruction. DOSAGE: 400 mg. May be repeated in 4 hours. After relief, lengthen the dose frequency. (see side note)

NOTE: *The high therapeutic index of Trocinate permits its administration in dosage sufficient to relieve smooth muscle spasm promptly. 400 mg. dosage usually creates a therapeutic blood level. In reducing dosage after relief, lengthening the time between dosage rather than lessening the recommended dose is preferable. The prompt direct action allows a consciousness of the first suggestion of return of symptom . . . a guide to dose spacing and to determining when treatment is complete. A prescription for twelve or sixteen 400 mg. tablets will usually correct spasm and leave a few tablets for a reserve.*

WILLIAM P. POYTHRESS & CO., INC.
RICHMOND, VIRGINIA 23217
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Didactic

Cerebral Infarctions

"Strokes" are the most common neurological disease occurring in our older patients. They come to the physician following a sudden failure of a part of their cerebral circulation which results in deficits of consciousness, vision, speech or sensory-motor function. If the insult is recent and severe enough to produce coma the medical man has become quite adept at returning such individuals to a more viable state. If, however, one considers the brain damage rather than its systemic manifestations, the physician is woefully lacking in effective tools to prevent, limit the extent or promote healing of a brain whose circulation is impaired. The location and the extent of the lesion determine the outcome and it is not altered by medical care; the survival and disability remain independent of medical care.

Factors as simple as diet or medicine may one day inhibit atherosclerosis and prevent "strokes" from occurring. Clot mechanism of blood may one day be changed by medicines which could prevent "strokes." Even today surgical removal of narrowed blood vessels of the neck may be preventing some "strokes" from occurring, but unfortunately it is rarely useful. Anticoagulants may prevent "strokes" from occurring in very select cases, but usually they are worthless.

The patients who develop a "stroke" and have a disability do not demand removal of the lesion or a "cure" for their damaged brain; they come only for "help." Too often, if the "help" required is not something dramatic, like the excision of the rare brain tumor, the miraculous "cure" of a brain abscess or the elevation of a depressed fracture; or if the need for maintenance of body function with mechanical respirators, potent hypertensive agents or parenteral electrolytes is not present, the "medical scientist" has no "help" to offer the patient. He may even deny the disability as a "medical challenge." The role of the physician suffers when medical "need" is met only with scalpels, a definite number of milliequivalents of a panacea or antibiotics. The "discomfort of man," whatever the cause, even that from the disability of cerebral vascular accidents, is still the "business" of medicine, and it deserves to be treated earnestly, and with dignity.

The inability to walk or to care for oneself is a catastrophic problem. Decreasing invalidism and aiding a human by any means possible is quite as dramatic as transplanting an organ and really much more needed.

In our flair for subspecialization the "Rehabilitation Centers" and the dedicated men who inhabit them may be impressive and competent; they use ingenious equipment and large "staffs" who help a few people function and feel better. This form of care unfortunately is seldom available or even needed by our oldsters who have their "strokes" in every community of our nation. They do not require extensive "testing" or "retraining" for vocations or even avocations; what they need is to relearn to walk and take care of themselves.

"The art of medicine" can again be employed; skills whereby the ill are made more comfortable can again become medical tools. Patients with "strokes" who can't walk, speak or care for themselves are ill, uncomfortable,

frightened, helpless humans who ask and need medical aid. Their initial difficulty is walking. They should be helped to ambulate as soon as their blood pressure can be maintained in the upright position. This often requires continuance of ambulation of a patient who limps into the office stating that his side was "weak" when he awakened that morning; it may be getting better but it still "isn't right." Walking would be far better than hospitalization and "absolute bedrest" for 10 days or six weeks until such patients really become invalided. Once hemiplegia occurs, a patient must be encouraged to relearn to walk with help as soon as medically feasible. A nurse and a doctor, or a nurse and the spouse can ambulate the most severe of hemiplegics and, when done repeatedly, this will result in the patient's ability to walk alone. The patient must be told that he is expected to walk; he must be encouraged. Patients have often been forced to battle against family, friends and even their physicians before being permitted to attempt walking; this is a far cry from the "art of good medicine."

A simple "pulley" and rope hung in any room can provide a means for strengthening the muscles and decreasing the spasticity of the involved extremities. Another aid for these patients is a simple mechanical device which holds up the toe of the involved foot. It attaches to the lower leg and the shoe on the involved side, dorsiflexing the weak foot that can cause the patient to trip. Encouragement and this "medical care" will get the oldest hemiparetic patient ambulating again. Independent walking gives these patients great comfort and greatly reduces the nursing care. The patient who walks to and from the table and the bathroom and who can come and go to his own room is far more "well" than if bedridden.

The patient's well-being is reflected in his family, nursing care and in a decreasing number of medical complaints. This philosophy of being able to help the patient even though you can do little to alter his pathologic process has been the mainstay of physicians since the beginning of time. The physician of today, when his scientific tools are no longer of any value, may still employ all of the "arts of medicine." "Stroke" patients are good patients to treat!

George C. Flora, M.D.
Minneapolis, Minnesota

In great consumptions learn'd Physicians thinke,
'Tis good a Goat or Camels milke to drinke,
Cowes-milke and Sheepes doe well, but yet an Asses
Is best of all, and all the other passes.*

*Regimen Sanitatis Salerni.

Editor's note: Here the School may well be taking a sly little dig at "learn'd" physicians for supposing that ass's milk surpasses that of cows, sheep, goats and camels in the treament of consumptions.

Men are very queer animals—a mixture of horse-nervousness, ass-stubborness and camel-malice.—Thomas Henry Huxley

I love my family.
I adore this house.
My in-laws are great.
The neighbors are wonderful.



Indications: For use in management of anxiety and tension occurring alone or as accompanying symptom complex to medical and surgical disorders and procedures. Though not a hypnotic, fosters normal sleep through antianxiety and related muscle-relaxant properties.

Contraindications: History of sensitivity to meprobamate.

Important Precautions. Carefully supervise dose and amounts prescribed, especially for patients prone to overdose themselves. Excessive prolonged use has been reported to result in dependence or habituation in susceptible persons, as alcoholics, ex-addicts, and other severe psychoneurotics. After prolonged excessive dosage, reduce dosage gradually to avoid possibly severe withdrawal reactions. Abrupt discontinuance of excessive doses has sometimes resulted in epileptiform seizures.

Warn patients of possible reduced alcohol tolerance, with resultant slowing of reaction time and impairment of judgment and coordination.

Reduce dose if drowsiness, ataxia or visual disturbance occurs; if persistent, patients should not operate vehicles or dangerous machinery.

Side Effects include drowsiness, usually transient, if persistent and associated with ataxia, usually responds to dose reduction; occasionally concomitant CNS stimulants (amphetamine, mephentermine sulfate) are desirable. Allergic or idiosyncratic reactions are rare, but such reactions, sometimes severe, can develop in patients receiving only 1 to 4 doses who have had no previous contact with meprobamate. Previous history of allergy may or may not be related to incidence of reactions. Mild reactions are characterized by itchy urticarial or erythematous maculopapular rash, generalized or confined to groin. Acute nonthrombocytopenic purpura with cutaneous petechiae, ecchymoses, peripheral edema and fever have been reported. One fatal case of bullous dermatitis following intermittent use of meprobamate with prednisolone has been reported. If allergic reaction occurs, meprobamate should be stopped and not reinstituted. Severe reactions, observed very rarely, include angioneurotic edema, bronchial spasms, fever, fainting spells, hypotensive crises (1 fatal case), anaphylaxis, stomatitis and proctitis (1 case) and hyperthermia. Treat symptomatically as with epinephrine, antihistamine and possibly hydrocortisone. Aplastic anemia (1 fatal case), thrombocytopenic purpura, agranulocytosis and hemolytic anemia have occurred rarely, almost always in presence of known toxic agents. A few cases of leukopenia, usually transient, have been reported on continuous administration.

Meprobamate may sometimes precipitate grand mal attacks in patients susceptible to both grand and petit mal. Extremely large doses can produce rhythmic fast activity in the cortical pattern. Impairment of accommodation and visual acuity has been reported rarely. After excessive dosage for weeks or months, withdraw gradually (1 or 2 weeks) to avoid recurrence of pretreatment symptoms (insomnia, severe anxiety, anorexia). Abrupt discontinuance of excessive doses has sometimes resulted in vomiting, ataxia, tremors, muscle twitching and epileptiform seizures. Prescribe very cautiously and in small amounts for patients with suicidal tendencies. Suicidal attempts have resulted in coma, shock, vasomotor and respiratory collapse and anuria. Excessive doses have resulted in prompt sleep, reduction of blood pressure, pulse and respiratory rates to basal levels; and occasionally hyperventilation. Treat with immediate gastric lavage and appropriate symptomatic therapy. (CNS stimulants and pressor amines as indicated). Doses above 2400 mg./day are not recommended.

Composition: Tablets, 200 mg. and 400 mg. meprobamate. Coated Tablets, WYSEALS® EQUANIL (meprobamate) 400 mg. (All tablets also available in REDIPAK® (strip pack). Wyeth.) Continuous-Release Capsules, EQUANIL L-A (meprobamate) 400 mg.

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Wyeth Laboratories
Philadelphia, Pa.

Photo professionally posed.



Special Article

Diabetes Detection and Education Center

A Regional Resource for the Practicing Physician

Education of the Patient with Diabetes Mellitus (A Vital Aspect of Medical Care)

DONNELL D. ETZWILER, M.D.; E. B. COHEN, M.D.†; DOROTHY VERSTRAETE, M.D., R.D.; FLORENCE R. RUHLAND, R.N., M.Ed. and JEAN ROBB

It is estimated that at the present time there are over 70,000 individuals with diabetes in the state of Minnesota. Patients with diabetes mellitus usually die of associated complications rather than of the disease itself; therefore its impact and importance in national health statistics is greatly underestimated. Diabetes mellitus currently represents the seventh leading cause of death in the United States and the third leading cause of blindness; and its close association with heart and blood vessel disease is well recognized. Diabetes is a chronic disease which cannot be cured at the present time, but can be controlled. Proper control, however, requires a close patient-physician relationship which must be fostered by mutual understanding and cooperation.

The medical profession requires the diabetic patient to assume a significant amount of responsibility for his disease. He must give his own insulin injections, regulate his exercise, choose his diet wisely, test his urine, and sometimes even alter his own insulin or oral hypoglycemic dosages. If patients are to assume these tasks, physicians must logically assume responsibility for patient education to insure that the tasks will be carried out properly and effectively. There can be no doubt that the well-informed, cooperative diabetic can decrease the incidence of acute problems to which he is susceptible, namely hypoglycemia and acidosis. Many authorities in the field of diabetes also feel that proper care may minimize or possibly eliminate some of the long-term complications frequently associated with this disease.

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†Adult Diabetes, Diabetes Detection and Education Center, Minneapolis, Minnesota. Internal Medicine, Physicians and Surgeons Building, Minneapolis, Minnesota.

Patient Education

Physicians must recognize patient education as a vital part of the quality medical care they must provide to the diabetic and his family. Education requires time, patience, and a great deal of repetitious effort. As students in medical school, we were exposed to the concepts of this disease in physiology, biochemistry, pathology, pediatrics, medicine, etc. As interns, residents, and practicing physicians, we periodically read and re-read about the disease. All too frequently, however, patients are given a brief explanation of the disease by their doctor, handed a drug-house manual or a book and told to learn about their condition. The new diabetic and his family members frequently say that the first few days after diagnosis and hospitalization are exceedingly traumatic, and this invariably limits their learning ability.

An effective educational program requires a significant amount of professional time and effort. Ideally, patient and family instruction should be a joint effort by physicians, nurses, dietitians, and other allied health personnel, each contributing in his own area of special skill and knowledge. Such programs, however, are rare and expensive to maintain. How then can a practicing physician provide the necessary in-depth instruction for individuals with diabetes and their families?

Objectives of the Program

After completion of several studies evaluating the effectiveness of patient education in this region of the country, a protocol for the establishment of a Diabetes Detection and Education Center was submitted to and approved by the U.S. Public Health Service in 1967.[2,3,4] Its objectives are four-fold:

1. To provide the practicing physician with a new resource center that can assist him in the management of his diabetic patients.
2. To improve the health of diabetic patients by stimulating their interest in and knowledge of their disease and management.
3. To establish an educational center where nurses, dietitians, and physicians can obtain comprehensive training in the management of diabetic patients.
4. To assist physicians in the early identification of the diabetic and to educate the general population in regard to the nature and prevalence of the disease.

Patient Classes

Patient classes are conducted at the Center every other week, with enrollment limited to 12 patients and their family members. This small number permits significant individualization in teaching and allows adaptation of a diabetic management program to the individual patient needs and living patterns rather than altering the patient's way of life to a rigid, uncompromising therapeutic schedule. Patients are referred by their private physicians, and a minimal tuition is charged. Upon acceptance, patients are asked to complete a biographical questionnaire which provides background information concerning management of their disease and living patterns.

Technique and Dosage

Patients arrive at the Center at 8:30 a.m. Monday morning and at 7:30 a.m. the following four days. Fasting blood sugar determinations are then obtained and second voided urine specimens are tested under the supervision of a nursing educator. One of the staff physicians then discusses with the patient the day's dosage of insulin or oral hypoglycemic agents and its rationale. Following this, patients who are able to give their own insulin injections are observed by the nursing staff, and their techniques and materials carefully assessed. New patients and their families are instructed, and demonstrations of proper technique are provided. Patients are requested to bring their own syringes and needles in order that the staff can evaluate their condition and use. The various possible injection areas are carefully outlined on each patient and individual site rotation charts made. Areas of hypertrophy and atrophy are pointed out, and the importance of avoiding repeated injection in these areas is stressed.

Diet Control

Patients then go to the cafeteria where they select their exchange diet under the direction of one of the staff dietitians. This has proven to be a valuable asset to the program. Too frequently in hospitals, patients are permitted to check off a list of their food likes and dislikes, and an appropriate tray is sent to their bedside. This provides little personal involvement and seriously limits the value of competent concurrent nutrition lectures and instructions. In the cafeteria, patients see the size of food portions and make diet choices as they view the food selections. This, in turn, reinforces the more didactic lecture material. After breakfast, patients proceed to the classrooms where lectures, demonstrations, and conferences are conducted throughout the remainder of the morning. Appropriate mid-morning breaks are scheduled, at which times snacks are provided and exercise is encouraged. Urine tests are again obtained at noon. After lunch, classes reconvene at 1:30 and last through 3:30, when the patient may obtain additional individual help or return to his home or one of the nearby community hospitals, motels or hotels.

Five days of concentrated instruction provides these patients with adequate time for a comprehensive approach and understanding of the basic nature of diabetes. The 44-hour schedule furnishes the fundamental information concerning diabetes and permits the patient and his family time to relate the material to their own situation. A significant portion of this time is also devoted to individual conferences and group discussions. The week's teaching schedule is shown in the Table.

TABLE

PATIENT SCHEDULE

Report Monday at 8:30 a.m. to the Diabetes Detection and Education Center for registration and distribution of materials.

Report Tuesday through Friday at 7:30 a.m. for urine testing, insulin instruction and administration.

Urine testing equipment and insulin will be provided at the Center. Please bring your own syringe if you are taking insulin.

Meals will be served Monday noon through Friday noon.

Breakfast .....8:15 a.m.
Lunch .....12:30 p.m.

Meal Planning at 12:00 noon and 3:30 p.m.

Class Schedule

Monday:		
9:00- 9:45	Introduction and objectives	Nursing Staff
9:45-10:15	Break and exercise	
10:15-11:00	What is diabetes? Current and changing concepts.	Dr. Etzwiler
11:00-11:45	Food for the diabetic	Nutrition Staff
11:45-12:00	Plan lunch	
1:30- 2:30	Insulin and oral hypoglycemic agents: their use in diabetes	Dr. Cohen
2:30- 4:00	Individual conferences	Nutrition and Nursing Staff
Tuesday:		
9:00-10:00	Acute complications	Dr. Sauls
10:00-10:30	Break and exercise	
10:30-11:05	Insulin administration—how and why?	Nursing Staff
11:05-12:00	How to plan your meals	Nutrition Staff
1:30- 2:15	Insulin administration (cont.)	Nursing Staff
2:15- 3:00	Urine testing	Nursing Staff
Wednesday:		
9:00-10:00	Personal hygiene	Nursing Staff
10:00-10:30	Problem solving	Nursing Staff
10:30-11:00	Break and exercise	
11:00-12:00	Exercise and its relationship to diabetes	Dr. Cohen
1:30- 2:15	Vocational planning: responsibility of the diabetic at work	Mr. Johnson
2:15- 3:00	Modifying your menu	Nutrition Staff
Thursday:		
9:00- 9:45	Food for special occasions	Nutrition Staff
9:45-10:15	Break and exercise	
1:15-10:45	Food for the sick day	Nutrition Staff
10:45-11:00	Pattern control	Dr. Etzwiler
11:00-12:00	Hereditary aspects and family planning	Dr. Barno, Dr. Slosser, or Dr. Mecklenburg
1:30- 2:30	Adjustment to diabetes	Nursing Staff
2:30- 3:00	The diabetic child—camp and school	Nursing Staff
	The diabetic eats out	Nutrition Staff
Friday:		
9:00-10:00	Long-term problems and complications of diabetes	Dr. Cohen
10:00-10:30	Film—"Understanding Diabetes"	
10:30-11:00	Break and exercise	
11:00-11:30	Course evaluation	
11:30-12:15	Research: New Developments. Hope for the future.	Dr. Maslansky
1:30- 2:30	Group discussion: Let's trade ideas	
2:45- 3:15	Lay societies: The community plays a vital role	
3:15- 3:30	Summary and presentation of certificates	

Comments

In our experience there is no one best teaching method or medium to be used with these patients; but by offering a great variety of lectures, audio-visual materials, group conferences, demonstrations, and the incorporation of other modern educational techniques such as teaching machines, etc., a rounded program is provided which complements and reinforces all vital aspects of diabetes management and care.

Advantages of a Community Center

A community center can provide in-depth programs that cannot be duplicated in individual hospitals. It permits wide usage of human community resources, such as representatives from the State Division of Vocational Rehabilitation, State Health Department, Department of Genetics, physicians practicing in the area with particular knowledge of diabetes as well as representatives from the University of Minnesota Medical School. Many patients who have had their disease for several years frequently say that they have a new understanding of their condition and that previously-learned isolated facts have now fallen into a logical sequence. Most patients have also commented that they wish they had had this course early in their disease; and it is fascinating to see the degree of self-confidence that new and old diabetics can gain at the end of a single week. Group discussions encourage and permit patients to see that their problems are not unique, and suggestions and comments from fellow students are valuable assets in the patient's acceptance of his condition.

Life-Long Problem

As previously stated, diabetes is a chronic disease which patients will live with for the remainder of their lives; hence physicians and other members of the health team must realize the important role patient education serves in permitting and stimulating proper management of the disease. Recently a physician commented that a "brittle" patient could not afford the time to attend a five-day educational program. Had the doctor seriously considered the chronicity of the disease with all of its possible acute and long-term complications, he would have realized that this patient couldn't



Group discussions



Instruction in insulin administration



Urine testing

afford not to spend five days learning about proper management of the disease.

The Diabetes Detection and Education Center was developed by practicing physicians to provide other physicians in this region with an educational resource for their patients with diabetes. At the end of the patient's five-day learning experience, detailed summaries are sent to referring physicians, describing the patient's knowledge and understanding of his condition. Various test scores and laboratory data are included as well as the patient's current insulin or oral hypoglycemic therapy and a complete evaluation of his diet. A general assessment of the family's understanding, acceptance, and motivation to carry out appropriate therapy is also provided. When individual patient problems are significant, these are also stressed and appropriate suggestions included. The patient is then returned to the care of the referring physician for his continued supervision and management.

For additional information on patient enrollment, write or call the Diabetes Detection and Education Center, 916 East Fifteenth Street, Minneapolis, Minnesota 55404. Phone: 332-2446.

More Light!

On March 15th (1832), in very bad weather, he (Goethe at 83 years of age) caught cold. Accustomed to close rooms, he often caught cold, and took no serious notice of the chill. He was feverish and kept to bed on the following day, but seemed to recover. On the night of the 19th, however, he found himself suddenly and violently attacked. His limbs were icy cold, his chest was racked with pain, and his face was drawn and grey with his sufferings. The physician found him in a very grave condition, and took such measures as would relieve the pain without promising recovery. On the following day he thought that he had returned to life, as the pain had ceased. He sat all day in the long easy-chair in the bedroom, vainly attempting to read and falling occasionally into a comatose condition.

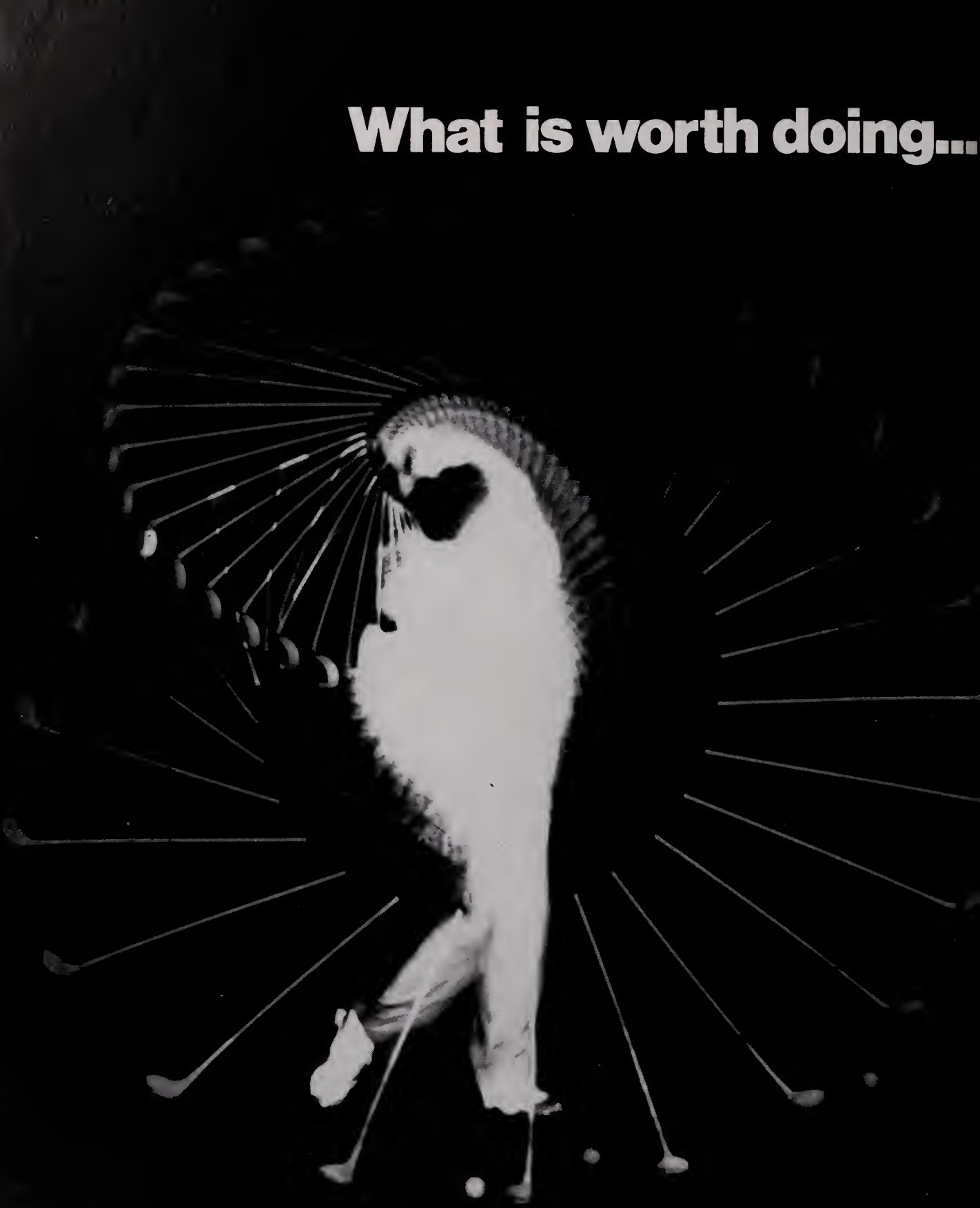
On the morning of the 22nd he was again removed to the chair at six o'clock, and was still persuaded that he was getting better. The few intimate friends spent the day with him, knowing that they were listening to the master's voice for the last time. Goethe did not know it. About nine in the evening he asked the date, and, rising again from his chair, said: "So spring has set in: I shall get better the more quickly." He sat down and fell asleep, moving and muttering in his dreams. "See the beautiful woman's head in colour, with black locks, on a dark ground," they heard him mutter. His theory of colour seemed to mingle in his mind with the paling figures of the women he had known.

In the morning he asked for a cold fowl for breakfast, and even ordered his dinner. He again tried to walk to the study, but failed, and returned to the chair, and the hours went by in drowsy condition, with half-conscious intervals. Shortly afterwards he said to his servant: "Open the second shutter also, so that we may have more light." It is from this sentence that the cry "More light" has been taken by those who would make it symbolical. He sank slowly and painlessly, in half-conscious state, trying to spell letters with his finger after the power of speech had gone. About midday he seemed to settle more comfortably in the corner of the chair, and when they presently looked at him, they found that he was dead.*

*Joseph McCabe: Goethe, The Man and His Character, 1912.

Silence is the unbearable repartee.—Gilbert Chesterton

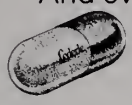
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Side Effects: Gastrointestinal system—anorexia, nausea, vomiting, diarrhea, stomatitis, glossitis, enterocolitis, pruritus ani. Skin—maculopapular and erythematous rashes (a case of exfoliative dermatitis has been reported); photosensitivity reaction, onycholysis and discoloration of nails (rare). Kidney—rise in BUN, apparently dose-related. Hypersensitivity reactions—urticaria, angioneurotic edema, anaphylaxis. In young infants, bulging fontanels have been reported following full therapeutic dosage. This symptom has disappeared rapidly when drug is discontinued. Teeth—dental staining (yellow-brown) in children of mothers given tetracycline during the latter half of pregnancy, and in children given the drug during the neonatal period, infancy and early childhood. Enamel hypoplasia has been seen in a few children. Blood—anemia, thrombocytopenic purpura, neutropenia, eosinophilia. Liver—cholestasis (rare), usually at high dosage. Tetracycline may form a stable calcium complex in bone-forming tissue. If adverse reaction or idiosyncrasy occurs, discontinue medication and institute appropriate therapy.
Average Adult Daily Dosage: One Gm. per day, in 4 divided doses of 250 mg. each. Should be given 1 hour before or 2 hours after meals, since absorption is impaired by the concomitant administration of high calcium content drugs, foods and some dairy products. Treatment of streptococcal infections should continue for 10 days, even though symptoms have subsided.

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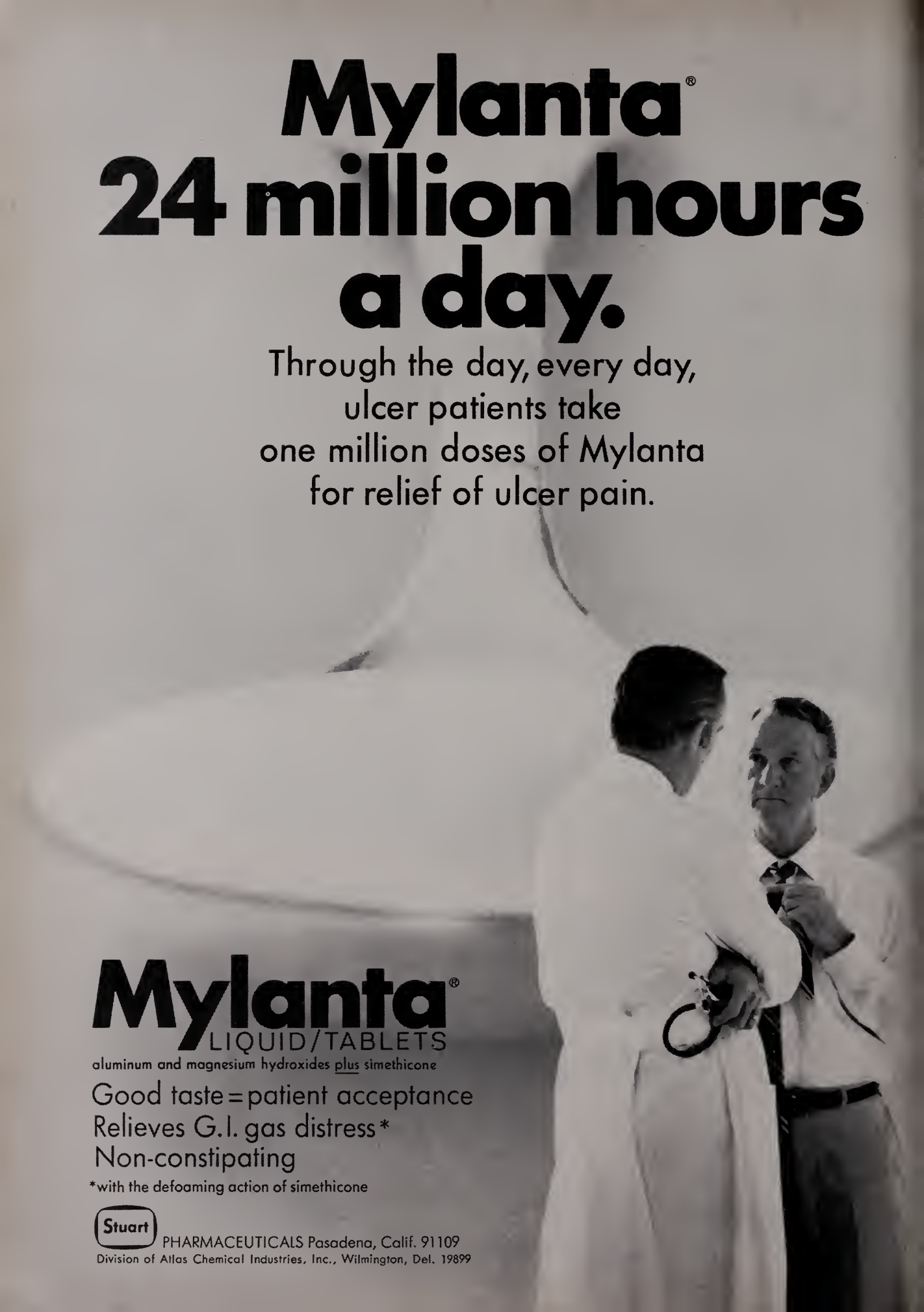
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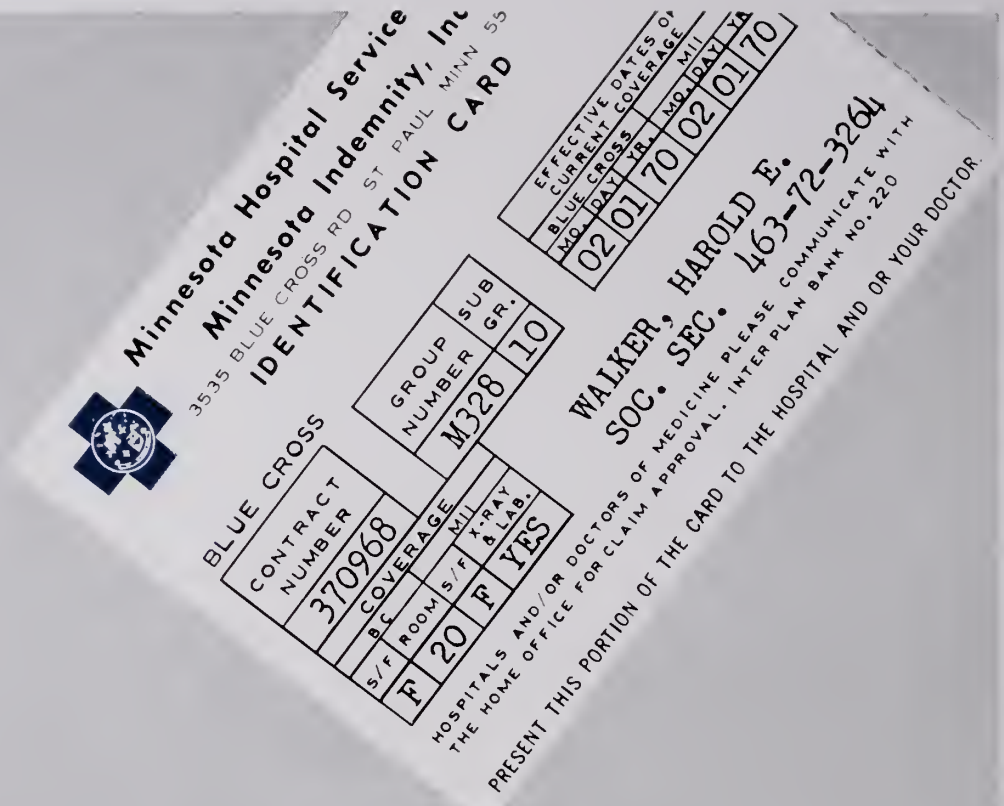

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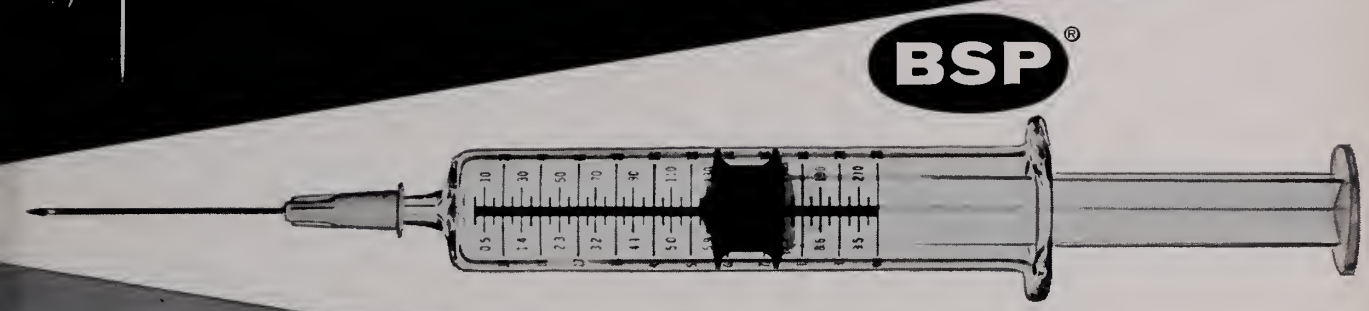
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Precautions: Do periodic serum electrolyte and BUN determinations. Do periodic hematologic studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in postsympathectomy patients. The following may occur: hyperuricemia and gout, reversible nitrogen retention, decreasing alkali reserve with possible metabolic acidosis, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), digitalis intoxication (in hypokalemia). Use cautiously in surgical patients. Concomitant use with antihypertensive agents may result in an additive hypotensive effect.

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President's Letter

I HAVE HAD THE privilege of serving on the boards of county and state health departments for the past 20 years. It has been a very satisfying and a great educational experience. I wonder how many physicians in Minnesota are aware that our State Board of Health was founded in 1872—the third in the nation, having been preceded only by similar bodies in California and Massachusetts.

Now, after almost 100 years of the existence of this state agency, it would seem appropriate to point out the good working relationship between the State Board of Health and the medical profession. There are many examples over the years of major benefits to all citizens from this cooperation.

In the recent rubella immunization program in Minnesota, endorsed and assisted by physicians in practice, our state led the nation in effectiveness. Only 10 of the 50 states were able to immunize at least 50% of their children. In Minnesota more than 90% of all children one year to 12 years old were immunized, and this was done at a very nominal cost to taxpayers. One of our neighboring states appropriated more than three quarters of a million dollars for an immunization effort, but that expenditure produced a much lesser percentage of children immunized than was achieved here.

It is not common knowledge that Minnesota was instrumental as early as 1957 in the development of poliomyelitis vaccine for oral administration, particularly the trivalent oral vaccine which was discovered in research studies authorized by the State Board of Health and conducted in the Division of Medical Laboratories of the Board. Many of you will recall the very extensive field trials conducted in 1960 with this oral vaccine. Results of the studies stimulated others working in the field of oral poliomyelitis vaccines, and contributed much to acceptance of this method of immunization.

Among officials of the Federal Government there is considerable concern regarding the quality of clinical laboratory work as related to payment for services rendered to persons treated under the provisions of the Medicare program. The Minnesota State Board of Health has been cognizant of the clinical laboratory problems since 1950 and, in cooperation with the Minnesota State Medical Association, the Minnesota Hospital Association, the Minnesota Society of Clinical Pathologists and Minnesota Society of Medical Technologists, instituted a proficiency-testing program, on a voluntary basis, in the field of laboratory work. In view of certain regulatory trends taking place at the federal level, it has become necessary to develop legislation concerned with laboratory practices in Minnesota. Once again, the state medical association, hospital association, clinical pathology and medical technology societies, and other professional laboratory groups have joined the State Board of Health in drawing up legislation which is unique in the United States and which will be introduced to the 1971 legislature.

In the next issue of MINNESOTA MEDICINE I shall point out other instances of how citizens of Minnesota have benefited by the cooperation of Minnesota physicians and the Minnesota State Board of Health. This special issue of MINNESOTA MEDICINE is dedicated to the University of Giessen located near Frankfort-on-the-Main, Germany. It is one of the first German medical schools to adopt American methods of teaching bedside medicine to small groups. It was here that many American physicians went abroad to study before the turn of the century.

Raymond J. Jackman, M.D., President,
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Splanchnicectomy in Chronic Pancreatitis

Application and Effect

K. VOSSSCHULTE, M.D.* and E. WAGNER, M.D.*

THE SURGICAL TREATMENT of chronic pancreatitis is directed against the *manifestation of pain* caused by the disease. It is true that chronic, continuous pain is distinguished clinically from recurrent attacks, but a correlation between these two types of pain and specific anatomo-pathological processes in the pancreas cannot be found. For this reason, it is not possible to deduce from the type of pain, the pathological processes or the operation of choice.

Removal of Obstruction

The method of treatment is clear only if calculi are found in Wirsung's duct on radiographs taken preoperatively. The same is true of cicatricial stenosis of the duct (sphincter sclerosis) although, in the opinion of the authors, this is a rare cause of chronic pancreatitis. In general, removal of the obstruction or, if this is not possible, a decompression procedure (anastomosis of the dilated duct with the intestine) is the only measure which can be applied in these patients. This system of treatment is so successful that other operative procedures are out of the question.

Similarly good results can be achieved in localised pancreatitis,† in which there is no obstruction of drainage, by resection of the diseased part of the pancreas. The best conditions are found when the symptoms are manifest in the tail of the pancreas even when the picture is complicated by pseudocysts. Resection of the diseased part of the gland usually eliminates the complaints and protects the patient from further complications. The same principle is applicable to the so-called "pancreatitis of the head." However, in the experience of the authors, both conditions are rare.

*From the Surgical Department of the University of Giessen (Director: Prof. K. Vossschulte).

†Pancreatectomy gauche after Mallet-Guy.

Splanchnicectomy

Clinical Indications

Although no discussion of the operative measures in the patho-anatomical forms mentioned above is necessary, surgical treatment of chronic *diffuse parenchymatous pancreatitis*—with or without disseminated calcification—which is not due to obstruction of drainage, i.e., when the entire gland is affected, is problematic. Operation on Wirsung's duct is pointless, and total pancreatectomy, with all its consequences, is out of the question in this benign disease, at any rate not as a primary procedure.

Modification of Splanchnic and Coeliac Ganglionectomy

In 1943 Mallet-Guy[3] suggested left-sided splanchnicectomy in order to remove the pain by interrupting the sensory supply of the pancreas. The operation was later extended to include the resection of the upper pole of the coeliac ganglion. This method has been hesitantly followed; it has been rejected by some and judged with reservation by others. The modifications suggested have hardly altered the situation. Smithwick[11] (1946) combined splanchnicectomy with sympathectomy. Grimson and co-workers[2] (1947) resected the coeliac ganglion and the vagus nerve in addition. Ray and Console[9] (1949) combined bilateral splanchnicectomy with resection of the sympathetic trunk. Yoschioka and Wakabayashi[14] (1958) suggested "post-ganglionic neurotomy." None of these modifications have had much support. The fact has finally emerged that our knowledge of the vegetative nervous system is still incomplete. This defect, in turn, affects the surgery of this part of the nervous

system in general. Apparently the anatomical variations are also numerous; otherwise many clinical observations could not be explained.

Nerve Pathways

It can be assumed that the vagus nerve possesses no pain-conducting pathways; therefore resection of the nerve cannot relieve the sensory pain in chronic pancreatitis. The phrenicoabdominal branches of the phrenic nerve, on the other hand, conduct afferent vegetative pathways which provide pain sensation to the peritoneum of the diaphragm, the liver, and the anterior wall of the upper abdomen. They are not affected by splanchnicectomy or resection of the coeliac ganglion, which explains in part the unsatisfactory results of visceral nerve resection. Care in indication appears to be more important. Splanchnicectomy is suitable only for the primary disseminated form of chronic pancreatitis. Experience has shown that pain in pancreatitis caused by obstruction cannot be relieved by procedures involving the vegetative nervous system. In addition, chronic alcoholism influences the results of the operation. These points are empirical and have no satisfactory explanation.

Cause-and-Effect Therapy

Mallet-Guy[3] regarded splanchnicectomy as a causal therapy in that the operation interrupted not only the pain-conducting paths but also the vasoconstrictor fibres which are activated by reflex from receptive cell aggregates in the pancreas. From this point of view, it is tempting to suggest a pathogenesis for chronic pancreatitis. However, the vicious circle: initial fibrosis—stimulation of the vegetative receptors embedded within the pancreas—vasoconstriction—destruction of the parenchyma—fibrosis—has not yet been sufficiently proved. In the experiments carried out in this hospital by Schönbach,[10] no vasoconstrictor fibres leading

TABLE I

Splanchnicectomy with and without Additional Procedures on the Vegetative Nervous System in Chronic Pancreopathy. Postoperative Period of Observation: Few Weeks to Several Years.

Author		No. of cases	Results	
			satisfactory	unsatisfactory
Fontaine and Mitarbeiter	(1946)	1§	1	—
Grimson and Mitarbeiter	(1947)	1§	—	1
Rienhoff and Baker	(1947)	1§	—	1
McDonough and Heffernon	(1948)	3†	3	—
Ray and Console	(1949)	5†‡	5[3]	—
De Takats and Mitarbeiter	(1950)	7†‡	6[3]	1
Connolly and Richards	(1950)	2†	2	—
Hurwitz and Gurwitz	(1950)	6†	6	—
Rack and Elkins	(1950)	3†	3	—
Bingham and Mitarbeiter	(1951)	1†	1	—
Hyman and Burton	(1951)	5†	1	4
Kment	(1953)	11‡	10	1
Morrissey	(1953)	2†	2	—
Pfeffer and Hinton	(1956)	5†	5	—
Ogle and French	(1956)	4†	4	—
Hess	(1959)	8§	2	6
Warren and Cattell	(1959)	9†	3	6
Howard and Jordan	(1960)	5†	—	5
Rossetti	(1963)	2‡	2	—
Burkhardt	(1963)	3‡	3	—
Salembier and Mitarbeiter	(1964)	27‡	16	11
Rhaods	(1965)	8‡	4	4
Sarles	(1965)	3§	—	3
Kourias and Papacharalampous	(1966)	15‡	12	3
Kyrle	(1966)	4‡	3	1
Total		141	94 (67%)	47 (33%)

*With simultaneous vagotomy
†With sympathectomy of varying extent (uni- or bilateral)
‡Left-sided or bilateral splanchnicectomy
§Left-sided splanchnicectomy

to the pancreas could be found in the splanchnic nerve. It was not possible to produce a pancreatitis by electrical stimulation of the nerve. The same results have been obtained by Menguy and co-workers[7] and by Möller.[8] Splanchnicectomy must be regarded primarily as a means of relieving pain in pancreatitis. Its causal value requires more study.

Results of Splanchnicectomy

It is difficult to obtain a uniform picture of the success of this operation from the statistics because of the anatomical uncertainty and the great variation in the extension of the surgical measure to include the visceral nerve supply. One must be content with approximations. Table 1 summarises 141 operations collected from 25 publications. Satisfactory results were obtained in 94 patients and disappointing results in 47. Two conclusions can be drawn from these figures:

1. The number of satisfactory results is twice as high as the number of failures.
2. The results of left-sided or bilateral splanchnicectomy cannot be improved by additional procedures on the sympathetic trunk.

If these statistics are limited to patients with more than one year of follow-up after operation (Table 2), there is little difference in the statistical results: 64% were satisfactory and 36% insufficient. White and co-workers[13] achieved 69% satisfactory and 31% disappointing results in a follow-up study on 39 patients operated five or more years previously. To date, the most successful results have been achieved by Mallet-Guy.[3] Out of 207 left-sided splanchnicectomies, 85% were reported as successful. The number was reduced to 67—75% in chronic alcoholism, depending on whether cirrhosis of the liver was also present.

These statistical reports are not free from the imperfections which the clinician must accept when trying to express his observations, findings, experience, therapy, and results in numbers. This reservation does not obscure

TABLE 2

Splanchnicectomy with and without Additional Procedures on the Vegetative Nervous System in Chronic Pancreopathy. Postoperative Period of Observation: 12 Months to Several Years.

Author		No. of cases	Results	
			satisfactory	unsatisfactory
McDonough and Heffernon	(1948)	3‡	3	—
Ray and Console	(1949)	3†‡	3	—
De Takat sand Mitarbeiter	(1950)	3†‡	3	—
Kment	(1953)	3‡	2	1
Pfeffer and Hinton	(1956)	5†	5	—
Ogle and French	(1956)	4†	4	—
Warren and Cattell	(1959)	9†	3	6
Howard and Jordan	(1960)	5†	—	5
Rossetti	(1963)	2‡	2	—
Burkhardt	(1963)	1‡	1	—
Salembier and Mitarbeiter	(1964)	17‡	10	7
Rhaods	(1965)	8‡	4	4
Sarles	(1965)	3§	—	3
Kourias and Papacharalampous	(1966)	15‡	12	3
Kyrle	(1966)	3‡	2	1
Total		84	54 (64%)	30 (36%)
Mallet-Guy in continued alcoholism	(1965)	207	85% 67-75%	15%
Postoperative observation time of five or more years				
White and coworkers	(1966)	39 (Pancreatic fibrosis*)	27 (69%)	12 (31%)

*The cases are classified according to the suggestion of Mallet-Guy (1959)
†With sympathectomy of varying extent (uni- or bilateral)
‡Left-sided orbilateral splanchnicectomy
§Left-sided splanchnicectomy

the prediction of the statistics which show that, although the results of splanchnicectomy in chronic fibrotic pancreatitis are not excellent, they are not so pessimistic as is often assumed. From the results quoted in publications, it can be stated that the operation is successful in two thirds of the patients if the rules for indication are observed.

From the anatomical studies by Ray and Console,[9] and by Clara,[1] it appears advisable to carry out bilateral resection of the splanchnic nerve and to resect the upper pole of the coeliac ganglion as Mallet-Guy[3] suggested several years ago in left-sided resection. Entry through a medial laparotomy of the upper abdomen allows control of the biliary tract and the drainage conditions in the pancreatic duct. Dilation of Wirsung's duct is not an indication for splanchnicectomy. In order to find the nerve, the aorta must be freed from the surrounding muscle fibres of the crura of the diaphragm. Figure 1 shows the topography and extent of the resection.

There were no postoperative complications. The patients could be discharged from hospital between the 10th and 21st postoperative days.

Observations

Between 1966 and September 1968, 11 patients (seven men and four women) underwent bilateral splanchnicectomy with resection of the upper pole of the coeliac ganglion (Table 3). In five cases the results were not successful but reasons for failure could be found or suspected.

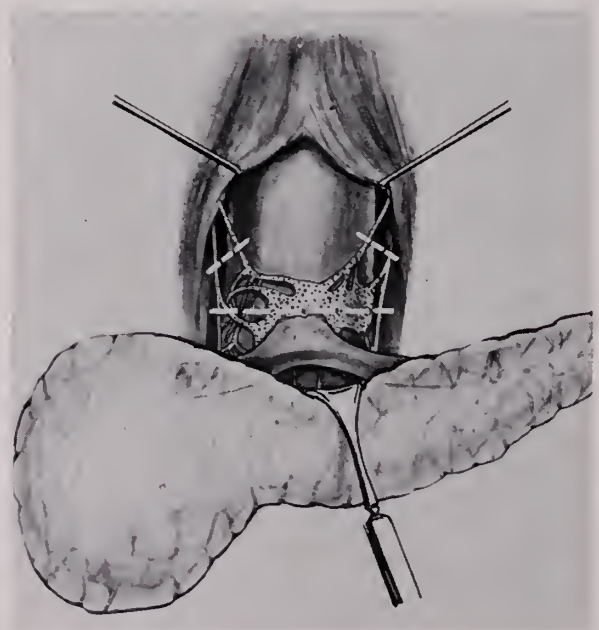


Fig. 1—Diagrammatic representation of the solar plexus with the large and small splanchnic nerves radiating left and right from the upper pole. The extent of resection of the coeliac ganglion is indicated.

In a 38-year-old female patient (Case 9 Table 3), the diagnosis of chronic pancreatitis was made by exclusion after extensive examination and observation. On operation, the pancreas was found to be normal macroscopically and on palpation; and this was confirmed histologically on a biopsy specimen. The cause of the continued symptoms has not been found in spite of renewed examination.

Failure Contributed by Alcoholism

In four other failures with renewed symptoms within one year of operation alcoholism played such a decisive role in the recurrence of pain that one cannot doubt the etiologic connections between the two factors. Two of this group (Cases 2 and 10) took to alcohol soon after the operation and the other two cases (7 and 8) remained free of pain until they returned to their old drinking habits. The further course of Case 7 has experimental significance in that the symptoms disappeared again when alcohol consumption was stopped, and the patient has now remained free of pain 17 months after operation. These observations support the published results from other hospitals and confirm that the success of splanchnicectomy is impaired by continued alcoholism. It is tempting to speculate in these cases that the alcohol stimulates production of the inflammatory parenchymatous reaction in the posterior wall of the abdomen, where it is transformed into a painful stimulus and conducted to the brain by way of the abdominal branches of the phrenic nerve. This hypothesis, however, cannot be proved.

Retroperitoneal Tuberculosis

Particular mention must be made of Case 4 (Table 3). This 30-year-old patient had a histologically confirmed pancreatitis. Pancreatectomy gauche was performed and the rest of the pancreas was anastomosed end-to-end with an isolated loop of the jejunum. Six months later, relaparotomy was necessary because of continuous pain. It was a surprise to find histologically-confirmed active tuberculosis of the mesen-

TABLE 3

Bilateral Spanchnicectomies with Resection of the Upper Pole of the Coeliac Ganglion

Patient Age (yr.)	Operation year	Operation	Operative finding Histological finds	Postoperative follow-up period (months)	Result of operation	Increase in Weight + —
32	1966	Bilateral splanchnicectomy with partial resection of the coeliac ganglion	Small nodular hardenings of the pancreas. Histology: chronic pancreatitis.	43	Free of pain. Occasional feeling of pressure after dietary error. Digestive disturbances.	10 kg —
34	1966	Left sided splanchnicectomy	Pancreas generally enlarged. Histology: slight chronic inflammatory changes.	39	Temporarily free of pain. New typical complaints of chronic pancreatitis. Alcoholism.	— 5 kg
26	1966	Bilateral splanchnicectomy with partial resection of the coeliac ganglion	Pancreas not significantly enlarged or hardened. No hist. examination.	35	Free of pain. Normal pregnancy and delivery.	15 kg —
30	1967	Bilateral splanchnicectomy with partial resection of the coeliac ganglion	Six months after pancreatectomy gauche. Remainder of pancreas unremarkable macroscopically and on palpation. Acute tuberculosis of the mesenteric lymph nodes. Histology: multiple tuberculous lymph nodules throughout the solar plexus.	33	Free of pain. Spastic sensations in upper abdomen.	10 kg —
57	1967	Bilateral splanchnicectomy with partial resection of the coeliac ganglion	Carcinoma of the head of the pancreas on the basis of a pancreatic fibrosis.	4	Free of pain until death, 4 months postoperatively.	died
57	1967	Bilateral splanchnicectomy with partial resection of the coeliac ganglion	Pancreas generally enlarged + Histology: lipomatosis of the pancreas.	17	Free of pain. Occasional diarrhoea.	5 kg —
35	1968	Bilateral splanchnicectomy with partial resection of the coeliac ganglion	Pancreas enlarged + small nodular hardenings.	17	Free of pain until 4 months postoperatively; after renewed alcoholism temporary return of symptoms (substitution with pancreatic enzyme preparations).	7 kg —
39	1968	Bilateral splanchnicectomy with partial resection of the coeliac ganglion	Pancreas generally enlarged + severely hardened. Histology: calcareous chronic pancreatitis.	17	Free of pain up to 1 year postoperatively; after renewed alcoholism, recurrent slight pain in upper abdomen—clinically chronic pancreatitis.	5 kg —
38	1968	Bilateral splanchnicectomy with partial resection of the coeliac ganglion	Pancreas unremarkable macroscopically and on palpation. Histology: normal pancreatic tissue.	15	No change in upper abdominal pain.	— 6 kg
35	1968	Bilateral splanchnicectomy with partial resection of the coeliac ganglion	Pancreas enlarged and hardened. Histology: chronic pancreatitis.	14	Free of pain until 10 weeks postoperatively. Attacks of pain after dietary error and alcoholism (chronic recurrent pancreatitis attacks).	2 kg —
38	1968	Bilateral splanchnicectomy with partial resection of the coeliac ganglion	Pancreas considerably enlarged and very resistant, particularly the head. Histology: pancreatic fibrosis.	13	Free of pain. Digestive insufficiency.	unchanged

teric lymph nodes. The remainder of the pancreas showed no clear signs of an inflammatory reaction or fibrosis. Resection of the splanchnic nerve was performed in the hope of relieving the pain. Apart from occasional spastic sensations in the upper abdomen, the symptoms have not reappeared since the operation 33 months previously. The patient has gained 10 kg in weight. Histological examination revealed finely disseminated tuberculous foci throughout the solar plexus. The retroperitoneal tuberculosis has since been healed clinically.

Case 3 has also been included in this series although the intraoperative findings did not correspond to a complete picture of chronic pancreatitis; clear induration of the pancreas and histological proof were missing. The patient was treated for more than a year as an out-patient because of continuous pain with sharp recurrent attacks. During hospitalisation, treatment was also unsuccessful. Since splanchnicectomy two years ago, the patient is free from symptoms and has gained 15 kg in weight. In addition, she had a normal pregnancy and delivery.

Discussion of the Results

Of the patients listed in Table 3, one (Case 5) died four months after splanchnicectomy of carcinoma of the head of the pancreas. He remained free of pain until death. The other patients were operated 13-43 months previously.

As we were interested in the therapeutic value of splanchnicectomy, patients 3 and 4 have also been included in Table 3 although the diagnosis of chronic pancreatitis was not confirmed. The success of the operation has now lasted more than two years in both cases.

The marked interference of alcoholism in splanchnicectomy can be seen both from the observation of Mallet-Guy[3] and the statistical results of White and co-workers.[12,13] This follow-up study was remarkable in that it could be shown that pain after operation due to alcoholism vanished if the patient gave up drinking.

A statistical analysis of the case histories summarised in Table 1 and 2 is surprising. Although there is no uniform operative method and uncertainties can creep into such a summary as in any other statistics of clinical observations, the calculations can be used for a general orientation. In the operated patients included in Table 1, the postoperative length of observation is approximately one year with 67% of successful cases. This result has hardly altered after a longer follow-up period (Table 2). Even the longer follow-up studies by White and co-workers[12,13] are of the same order. Apparently splanchnicectomy is more efficacious than is often assumed.

As far as can be deduced from the case histories and studies by Mallet-Guy,[4] resection of the coeliac ganglion is being included increasingly frequently in the operation. It appears to be doubtful whether the results can be improved still further by procedures on the sympathetic trunk. The published results rather suggest the contrary.

Control of pain by resection of parts of the nervous system is always a problem for the surgeon. Chronic pancreatitis is no exception. It was also difficult in this study to overcome the scepsis and decide on splanchnicectomy, but there appeared to be no other solution. The results obtained, however, did not correspond to the desperate picture of a hopeless experiment in treatment, but rather to that of a justifiable procedure.

Finally, it should be noted that the results of operation recorded 12 months after surgery do not change significantly over a period of several years.

Summary

In recurrent attacks of pain or continuous pain due to chronic pancreatitis resulting from obstruction of secretion, removal of the obstruction or decompression by pancreo-intestinal anastomosis is an efficient surgical therapy. In the rare cases of the localised primary parenchymatous form of the disease without obstruction of drainage, resection of the diseased part of the pancreas can be successful. When the disease is disseminated throughout the entire organ without dilation of the ducts, operation on the pancreas or ducts is not promising. Total pancreatectomy cannot be regarded as an adequate procedure. It can be avoided, however, by resection of the afferent conducting nerves of the splanchnicus system

as recommended by Mallet-Guy.[3] Statistical results have confirmed that the operation is satisfactory in two thirds to three fourths of the patients. Continued alcoholism considerably reduces the beneficial effect of splanchnicectomy.

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Overpopulation as A Form of Pollution

Concerning large families William Vogt, in a chapter titled "The Ethics of Parenthood" in his book, "People," says:

"Does the wealthy American family have a right to large numbers of children, simply because it is rich, because it can take care of them? The rich, as well as the poor, use water. They pollute our rivers and our air. They fill up space. They probably occupy more square yards of road per capita than less prosperous individuals, since they tend to use larger cars. And they are heavier consumers of resources, especially scarce resources."*

Editor's Note:

Furthermore, I ask: Is not their public education being subsidized by those who restricted their families? Is it fair that such excess children should constitute tax exemptions for their parents? Perhaps parents, rich and poor alike, with more than two or three children should be taxed for the education of any additional offspring. Strong medicine? Maybe so! But how else can irresponsible breeding be discouraged and checked?

Should not child-bearing no longer be regarded as an individual right, but rather as a social privilege contingent on the optimum good of the total group? Should not failure to comply with social sanctions be penalized by compulsory sterilization?

*William Vogt: People! Challenge to Survival, 1960.

Thought

The human tongue is only inches from the brain, but when you listen to some folks they seem miles apart.—M. Dale Baughman: Treasury of Stories.

The Voyage of Life

In the midst of the current of life was the Gulf of INTEMPERANCE, a dreadful whirlpool, interspersed with rocks, of which the pointed crags were concealed under water, and the tops covered with herbage, on which EASE spread couches of repose, and with shades where PLEASURE warbled the song of invitation. Within sight of these rocks all who sailed on the ocean of life must necessarily pass. REASON, indeed, was always at hand to steer the passengers through a narrow outlet by which they might escape; but very few could, by her entreaties or remonstrances, be induced to put the rudder into her hand, without stipulating that she should approach so near unto the rocks of PLEASURE that they might solace themselves with a short enjoyment of that delicious region, after which they always determined to pursue their course without any other deviation.

REASON was too often prevailed upon so far by these promises, as to venture her charge within the eddy of the Gulf of INTEMPERANCE, where, indeed, the circumvolution was weak, but yet interrupted the course of the vessel, and drew it, by insensible rotations, towards the center. . . . Those few whom REASON was able to extricate generally suffered so many shocks upon the points which shot out from the rocks of PLEASURE, that they were unable to continue their course with the same strength and facility as before, but floated along timorously and feebly, endangered by every breeze, and shattered by every ruffle of the water, till they sunk, by slow degrees, after long struggles and innumerable expedients, always repining at their own folly, and warning others against the first approach of the Gulf of INTEMPERANCE.

But such as had often fallen against the rocks of PLEASURE commonly subsided by sensible degrees, contended long with the encroaching waters, and harassed themselves by labors that scarce HOPE herself could flatter with success.

As I was looking upon the various fate of the multitude about me, I was suddenly alarmed with an admonition from some unknown Power, "Gaze not idly upon others when thou thyself art sinking!" I looked, and, seeing the Gulf of INTEMPERANCE before me, started and awaked.*

*Samuel Johnson (1709-1784)

Check-ups

Three foreign doctors were discussing a woman who had just had a miscarriage. "It's a shame, but she's impregnable," said one. "I'm afraid," said the second, "that isn't correct English; she's inconceivable." "Oh, no," said the third, "you're both wrong. She's unbearable."*

*Mark Wachs

How Not To Reach the Top

You'll never get to the top if you make a practice of blowing yours.—North Carolina Education.

Don't make excuses—make good.—Elbert Hubbard

The Postoperative Carbohydrate, Nitrogen, Fat and Electrolyte Metabolism*

Aldosterone-Blocking Agent Effect

K. SCHULTIS, M.D.†, C. A. GESER, M.D.† and E. WAGNER, M.D.†

During the past several years the terms "stress," "alarm reaction," "emergency reaction" and "total vegetative shift" have become part of the pathophysiological terminology. They describe the reactions of the organism to severe stress. If these reactions become too strong, it is sometimes considered necessary to initiate therapy. Many investigators have attempted to determine whether these reactions could be the cause of irreversible shock.[14,7,10,8] Some or all occur as a result of trauma or surgery; they are more or less pronounced, depending on the condition of the patient.

Aldosterone Production

Increased

The decrease of the Na/K quotient in the urine is considered a sign of increased aldosterone production.[18,6]

This condition is also found in patients with ileus,[11] portal hypertension[17] or acute tetanus.[16] During investigations, in collaboration with Dr. L'Allemand, on the problems of administration of food to tetanus patients during the intensive-care phase, we found that the catabolism was most pronounced in these patients. All of them had decreased Na/K quotients.

Decrease

An improvement of the Na/K quotient was achieved with i.v. administration of the aldosterone antagonist; the N-content and general condition of patients were also improved (decrease of the susceptibility to seizure). At present we do not know whether the aldosterone antagonist has a specific effect on the tetanus toxin.

Patients with Tetanus

Figure 1 shows values of three phases of administration of nourishment to a patient with tetanus. An increase of the Na/K quotient above 4 and a decrease of the N and K excre-

sex	diagnose	No. of days of therapy	bodywt., kg	admin. N in g/kg	admin. Cal/kg	Na:K in the urine	Level N in g/Tag	Level K in mval/Tag	remarks on feeding
m	Tetanus								
	I. Phase	21	70	0,23	25	0,89	-21,5	-56,5	Aminofusin 850, Fruktose, 200 ml Humanalbumin 20 %, Elektrolytkonzentr.
	II. Phase	7	54	0,29	35	4,96	-11,1	- 4,2	Aminofusin 850, Xylit Aldadiene-Kalium 400 mg/day
	III. Phase	7	52	0,47	58	1,62	+0,05	- 1,16	Aminofusin 850, Sonde: Biosorbin Aldadiene-Kalium 400 mg/day

Fig. 1—Sixteen-year-old boy with tetanus.

*This paper was presented at the Symposium from Postoperative Electrolyte and Fluid Shifts, Karlsruhe (Germany), November, 1967. F. K. Schattauer Verlag Stuttgart (New York 1968).

†From the Surgical University Clinic Giessen (Dir.: Prof. Dr. K. Vossschulte) and from the Medical University Policlinic München (Dir.: Prof. Dr. W. Seitz).

tion were achieved with aldadiene-potassium therapy (i.v.). We observed equal results in four additional patients with severe tetanus.

The effect of the aldosterone antagonist on the N and K metabolism in patients with tetanus, as well as the advantageous effect on K metabolism during the immediate postoperative phase, prompted our decision to conduct further studies on the effect of this drug on various metabolic values. During the past one and one-half years we administered the medication to patients during the post-traumatic phase. Some of our patients received the drug before surgery.[15]

Patients Having Surgery

Figure 2 shows the mean Na/K quotients of urine in patients with different types of abdominal and cardiovascular surgery (average dose: 200 mg. 3 × per day). The Na/K quotients of 63 patients were measured regularly. In patients without therapy fluid replacement was done with Ringer's solution, mean value 2.5 liters; the K excretion decreased noticeably during the first three postoperative days, as compared to the last two preoperative days. The quotient decreased; considerable Na retention occurred.

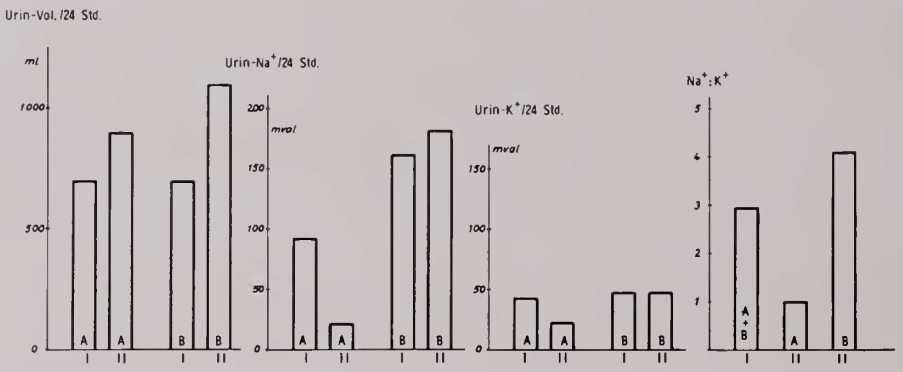


Fig. 2—Mean water, Na and K-excretion in 24 hours urine, pre and postoperative and mean Na-K quotient. A Ringer's solution; B Ringer's solution + 3 × 200 mg/. Tg. Aldadiene-Kalium; I preoperative; II 1.-3. Tg. postoperative.

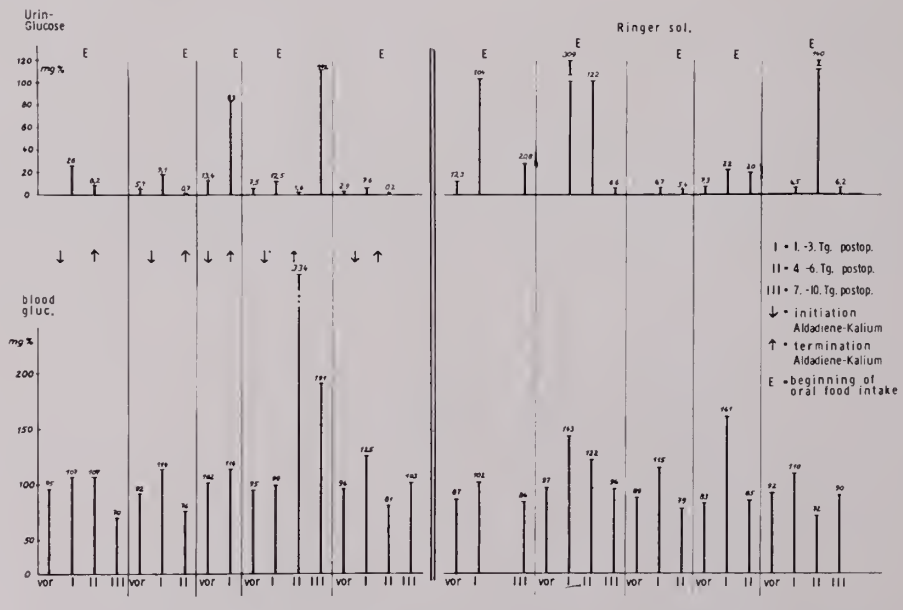


Fig. 3—Urine-glucose and fasting blood glucose, pre and postoperative under: Ringer's solution and aldadiene—potassium.

In patients with therapy the postoperative Na excretion increased; the K excretion remained constant. There was a definite effect of aldadiene-potassium on the quotient. Twenty-four-hour urine volumes increased during the first three postoperative days. Na increases the angiotensin sensitivity of the vessel walls, and this mechanism has a definite significance in cases of impending shock. Therefore it has to be determined whether the normally occurring Na retention during stress should be treated.

The increase of the Na/K quotient was accompanied by an advantageous effect on the intracellular K metabolism.[9] Therefore an effect of aldadiene-potassium on the glucose metabolism had to be expected. In 1965 Conn[4] reported a decreased carbohydrate tolerance in 50% of his patients with primary aldosteronism. Male patients under 50 years of age, with surgery for benign gastric or gallbladder disease, were treated; these patients did not have preoperative cardiac or circulatory disease, obesity, hepatic or renal insufficiency. Preoperative tolbutamide tests and i.v. glucose-tolerance tests were made.

Pre and Postoperative Blood Sugar

Figure 3 shows fasting glucose values in the blood of patients after surgery, as compared to the preoperative phase. These patients had hyperglycemia during the first three postoperative days (longer duration in some patients). Some patients developed glucosuria (top of diagram). These changes were less pronounced in patients with aldadiene-potassium therapy; however, if the therapy is discontinued prematurely, this phenomenon can occur at a later time. The time of initiation and termination of aldadiene-potassium therapy is shown by the arrows in the diagram.

Blood and Urine Sugar

This finding is repeated (summarized) in Figure 4. The increase of the fasting blood glucose concentration (postoperatively as compared to preoperatively) and the increase of renal glucose excretion over a period of 24 hours (postoperatively as compared to preoperatively) are shown in percentages.

Findings on the disturbance of glucose utilization after trauma have been published.[15] The i.v. glucose-tolerance test described by Conard,[4] for the testing of glucose-assimilation makes it possible to measure the capacity for the utilization of glucose. After injection of .33 g glucose/kg body weight i.v., capillary blood samples are taken every five minutes over a period of 30 minutes, for the glucose determination.

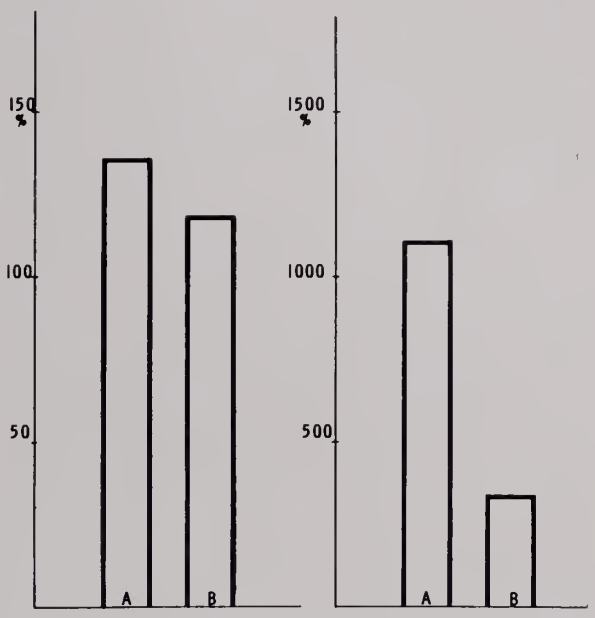


Fig. 4—% increase, postoperative compared to preoperative, for fasting blood glucose and urine glucose over a period of 24 hours. A Ringer's solution; B 3 × 200 mg Aldadiene Kalium.

K_G Values

From these values, the elimination constant K_G according to Dost[5] can be calculated. Results of this method of testing (five patients with, five without aldadiene-potassium therapy) are listed in Figure 5. The upper part of the diagram shows the K_G values of patients with Ringer's solution. These values decreased after the surgery. Only one of the five patients treated with aldadiene-potassium (Case 3) experienced this decrease. In Cases 4 and 5 the decrease occurred after the discontinuance of aldadiene-potassium therapy. Patient 1 had been living on an insufficient diet the last three months before admission to the clinic because of pyloric stenosis; his K_G value before surgery was .65 (lower limit: >1). A K_G of 1.54 was reached on the second postoperative day. If we consider that patients listed on the bottom

did not receive exogenous calories, it becomes clear that the primary reason for the glucose utilization disturbance can not be the postoperative hunger phase. The return of the K_G values to normal, independent of the diets of the patients, as well as the fact that there were no restrictions of food intake in the patients with fractures, speaks in favor of this theory.

The possibility of insufficient insulin production as a cause of the glucose utilization disturbance after stress was discussed. However, Ross and collaborators,[13] and our own radioimmunological determinations of insulin in collaboration with Dr. Geser, Munich,[15] disproved this theory.

Insulin Values

Figure 6 shows the average pre and postoperative insulin values of patients without therapy, those with glucose, those with xylitol, and those treated with aldadiene-potassium. The patients treated with carbohydrates received 100 g of the substrate 24 to 12 hours before examination. The right side of the diagram shows the increase (in %) of insulin activity in the serum 10 minutes after the injection of .33 g glucose/kg body weight for the Conard test. The average fasting values for the insulin activity were increased postoperatively, as compared to the preoperative phase

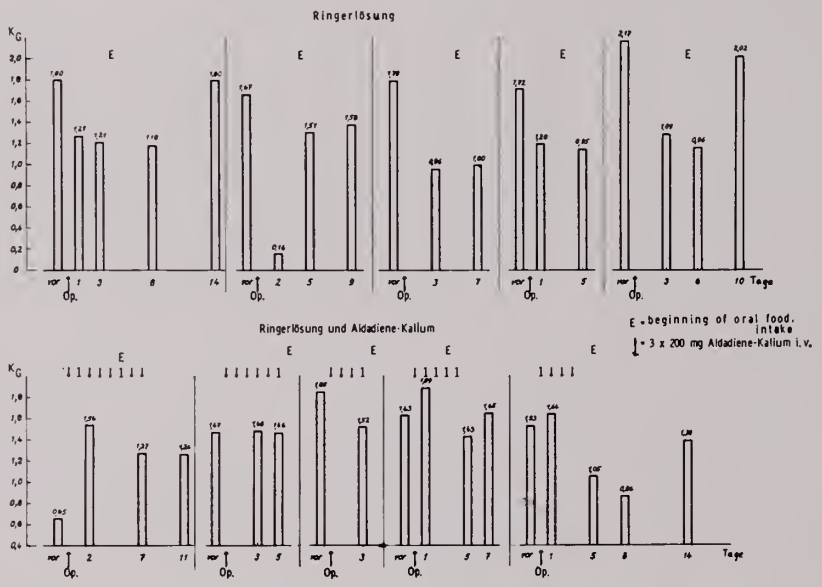


Fig. 5—Upper: Pre and postoperative K_G-values in five patients with Ringer's solution. Lower: Ringer's solution and aldadiene-potassium in five patients.

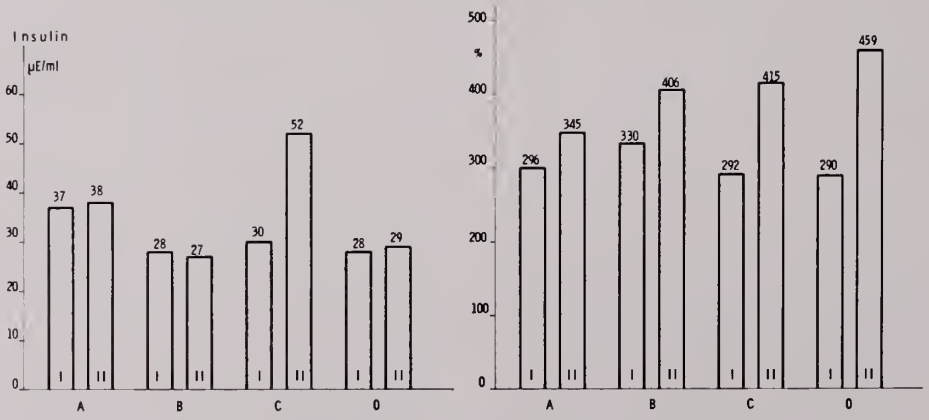


Fig. 6—(Left) Serum insulin pre (I) and postoperative (II-first to third day), postoperative therapy with: A Ringer's solution; B 100 g Glucose/24^h i.v.; C 100 g Xylit/24^h i.v.; D 3 × 200 mg Aladadiene-Kalium/24^h and (Right) Increase of serum insulin 10 minutes after glucose injection pre (I) and postoperative (II-first to third day); postoperative therapy with: (same key definitions as for left figure).

in the patients treated with xylitol. In all patients the reaction to the glucose injection was stronger postoperatively than before surgery. This increased readiness for insulin secretion to the adequate stimulant was most intensive in the patients treated with aldadiene-potassium. At the present time we are unable to fully interpret this finding.

Nitrogen-Saving Effect

An N-saving effect was not observed under aldadiene-potassium therapy; thus an advantageous situation for the protein synthesis did not exist. Figure 7 shows the differences of N-excretion between pre and postoperative phases in all groups. In a comparison with the controls, under glucose, the average N-loss was reduced from 7.8 g/24 hours to 5.2 g/24 hours <—>; under xylitol it decreased to 2.9 g/24 hours. Under aldadiene-potassium therapy the value did not change. The utilization of the endogenous glucose was improved with aldadiene-potassium therapy, as shown in a comparison of the low postoperative hypoglycemia and glucosuria values with the N-excretion.

Glucose Utilization

Figure 8 shows the glucose utilization under different conditions. In untreated patients and those treated with glucose the K_G values decreased from nearly 2 before surgery to 1.02 during the first three postoperative days. The decrease of K_G values in the patients treated with xylitol was noticeably less. These values did not decrease in the patients treated with aldadiene-potassium. However, the mean preoperative K_G value in the latter group was lower in comparison to the other groups, because the patient was included in the calculation of the mean value with a pathologically low value of .65. Nevertheless, a comparison with the other groups, excluding the patient with the low value, showed that there was only a very slight decrease of K_G value in this group.

Studies on the intermediary metabolism, under normal as well as pathological conditions, especially in cases of diabetes mellitus, showed similar results.

Our findings on the effect of the above mentioned carbohydrates on the post-traumatic metabolism point to a close relationship between the glucose utilization and the metabolites of the fat metabolism (measurable in the blood).

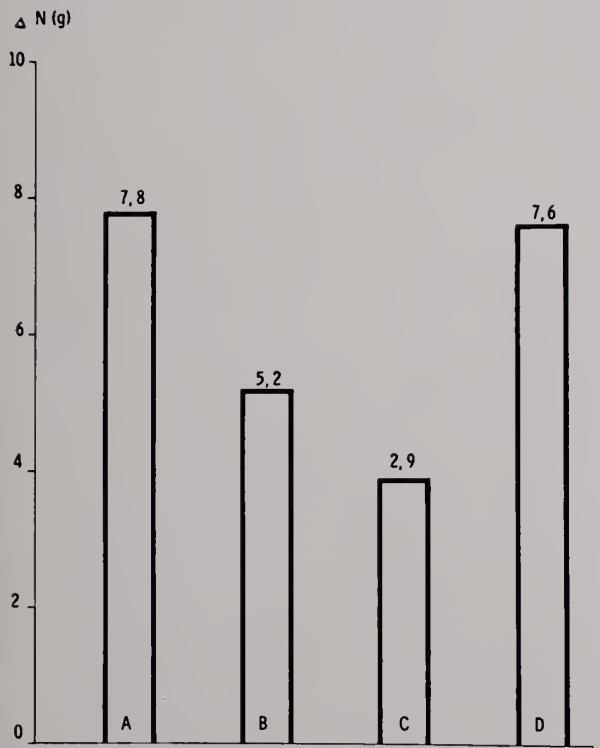


Fig. 7—Mean N-Loss ΔgN (Δ = mean postoperative urine N per day minus average daily preoperative urine N) A Ringer's solution; B 100 g Glucose/24h i. v.; C 100 g Xylit/24h i.v.; D 3 × 200 mg Aldadiene-Kalium/24h.

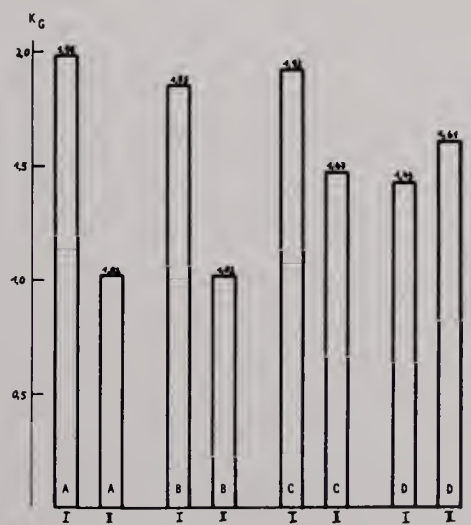


Fig. 8—Mean K_G-values, pre (I) and postoperative (II-first to third day), under postoperative therapy with: A Ringer's solution; B 100 g Glucose/24h i. v.; C 100 g Xylit/24h i.v.; D 3 × 200 mg Aldadiene-Kalium/24h.

Ketone Bodies

Figure 9 shows the ketone bodies. In our experience these are the most sensitive criteria for the fat metabolism measurable in the blood. Normally, an increased fat metabolism is considered the cause of ketosis (excessively high values). The part of the so-called ketoplastic amino acids can not be of significance, quantitatively. Rodewald[12] proved an increased fat metabolism to cover the energy need, by means of RQ measurements. Carlson[2] found a considerable increase of the nonesterified fatty acids in patients with extensive burns. The diagram shows the pre and postoperative total of acetacetate and β-hydroxybutyrate values for the four groups of patients. Fasting values as well as 10, 30 and 60 minutes after injection of .33 g glucose/kg body weight are listed. The ketosis was most pronounced in the patients with Ringer's solution (A). We have shown, in collaboration with Dr. Geser, that the development of this ketosis (statistical evaluation with the t-test) was significant in groups A and B.[15] Ketosis was not found in the group with xylitol therapy; aldadiene-potassium therapy has only a slight effect on the ketosis. Fasting values were comparable to the values in the group with glucose therapy.

Fatty Acids

Following are values of metabolites in the serum or blood. Figure 10 shows the nonesterified fatty acids (UFS) under equal testing conditions (as described for ketonemia). A comparison between the pre and postoperative situation shows hardly any difference (all groups). This finding was surprising and is a contradiction to the theory that stress produces an increased lipolysis. However, since we took our comparative values from the preoperative phase in patients who had fasted at least 14 hours, the relatively high preoperative values are understandable. At that, it should be considered, that the mean half-life for the nonesterified fatty acids is approximately three minutes and that the increased lipolysis is accompanied by an increased "turnover." This seems to explain the fact that we found no changes of non-esterified fatty acids in the serum in any of the groups. Seiler proved that the nonesterified fatty acids of rabbits during shock are analogous to human values.

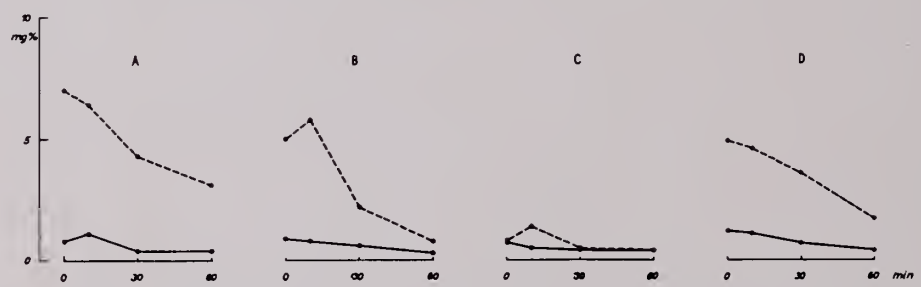


Fig. 9—Σ Ketone (Acetacetate + β-Hydroxybutyrate) in the blood fasting and 10, 30, 60 minutes after glucose injection (meanval.)preoperative (———); postoperative (- - - - -); 1.3. Tag; under postoperative therapy with: A Ringer's solution; B 100 g Glucose/24h i. v.; C 100 g Xylit/24h i. v.; D 3 × 200 mg Aldadiene-Kalium/24h.

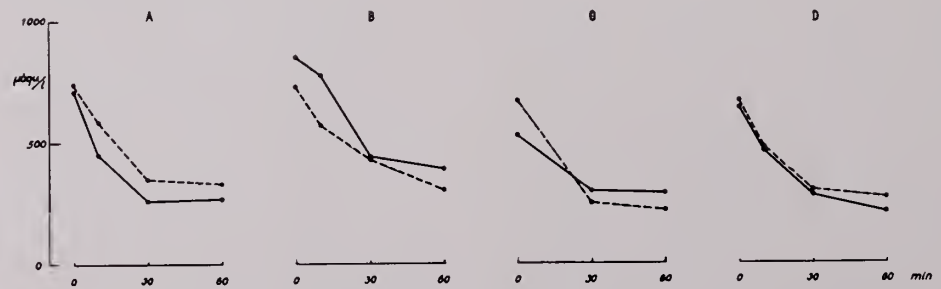


Fig. 10—UFS im Serum-fasting, and 10, 30, 60 minutes after glucose injection (meanval.); preoperative (———); postoperative (- - - - -); 1.-3. Tag; under postoperative therapy with: A Ringer's solution; B 100 g Glucose/24h i. v.; C 100 g Xylit/24h i.v.; D 3 × 200 mg Aldadiene-Kalium/24h.

Free glycerin

There was no increase of non-esterified fatty acid levels in our patients. Figure 11 shows the free glycerin values, which in all four groups decreased during the postoperative phase. Glycerin is a more sensitive indicator for the lipolysis thn the non-esterified fatty acids. This is proven by the fact that non-esterified fatty acids can enter re-esterifying from the lipolysis of glycerophosphate is available from the carbohydrate metabolism, while glycerin after total hydrolysis is flushed out of the fatty tissue and thus is not usable for re-esterifying. This means that with increased lipolysis, a decreased glycerin level proves an increased "turnover." Exact values of the decrease of the glycerin level in the different groups could not be calculated; however, a tendency toward such a decrease was clearly apparent in the patients treated with aldadiene-potassium. In our opinion the improvement of the glucose utilization under xylitol therapy on the total energy metabolism is produced by an advantageous effect. We believe that the improvement achieved with aldadiene-potassium therapy may be attributed to regulation of the transport mechanism. Xylitol therapy had a noticeable N-saving effect which was not observed under aldadiene-potassium therapy.

Triglycerides

Figure 12 shows the values of the serum triglycerides (equal conditions). Postoperative

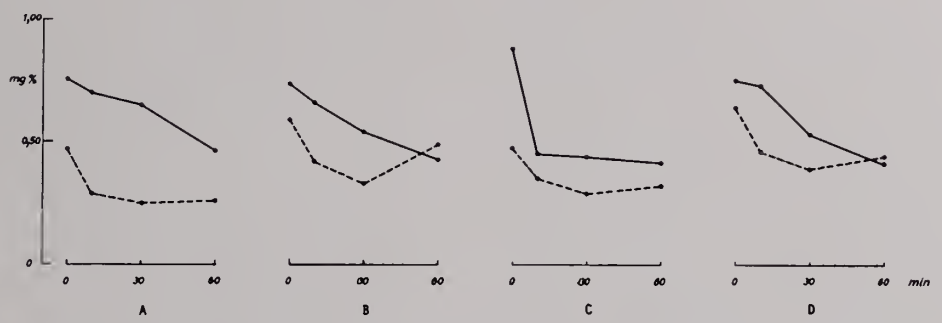


Fig. 11—Free glycerin of serum fasting and 10, 30, 60 minutes after glucose injection (meanval.); Preoperative (————); postoperative (- - - - -); 1.-3. Tag; under postoperative therapy with: A Ringer's solution; B 100 g Glucose/24h i.v.; C 100 g Xylit/24h i.v.; D 3 × 200 mg Aldadiene-Kalium/24h.

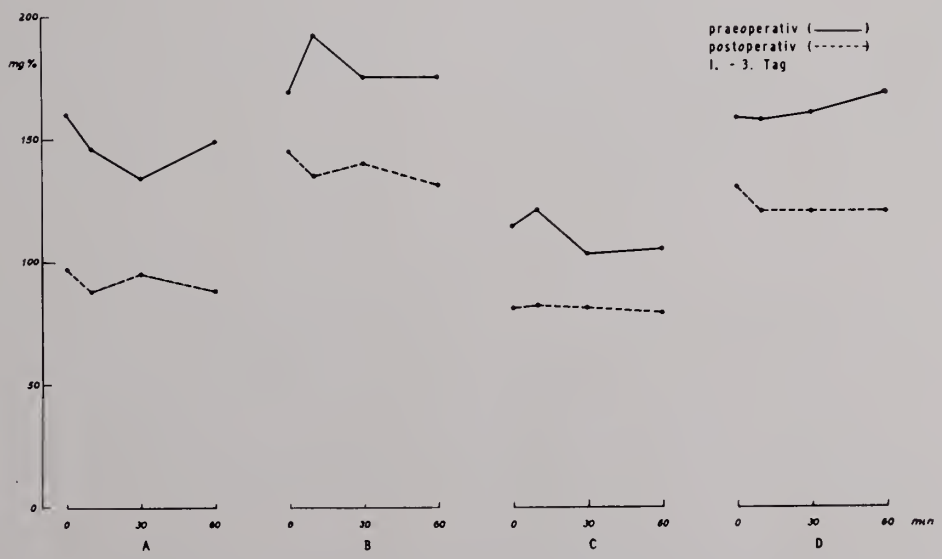


Fig. 12—Triglycerin of serum fasting and 10, 30 and 60 minutes after glucose injection (meanval.); under postoperative therapy with: A Ringer's solution; B 100 g Glucose/24h i.v.; C 100 g Xylit/24h iv..; D 3 × 200 mg Aldadiene-Kalium/24h

serum levels were noticeably below the preoperative values. We believe that their formation in the liver was decreased, which can be explained by the increase of the "turnover" for non-esterified fatty acids during the postoperative phase.

The effect of aldadiene-potassium on the postoperative metabolism was as follows:

1. Normalization of the Na/K quotients which had decreased during the postoperative phase.
2. Improvement of utilization of endogenous and exogenous glucose.
3. Increase of the insulin production after adequate stimulation, without effect on the fasting insulin values.
4. No effect on the fatty metabolites of the blood.
5. In cases of tetanus, aldadiene-potassium with simultaneous parenteral administration of amino acids and carbohydrates produced an improvement of the N levels.

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ISOLATION

The physician today must aspire to heal not the *sick* man, but the *man* sick, and must always offer him relief, counsel, and guidance for his return to the society from which his ailment has isolated him. Let us not forget that the most tragic feature of disease is that it *isolates* the patient. . . . In so doing, in separating him from the society to which he belongs when healthy, disease, now as yesterday, injects into the life of the patient an element of fate and eternity, a religious or philosophical faith—or lack of faith.*

*Felix Marti-Ibanez, M.D.: The Patient's Progress, 1962.

Editor's Note: Our very wise, valuable, honorable and expendable senior peers who must, perforce, retire from active life probably develop the same philosophy.

Electroencephalographic Findings in Heart Surgery

R. LORENZ, M.D.* and F. HEHRLEIN, M.D.*

CEREBRAL DYSFUNCTION is one of the most serious complications both during and after heart surgery. The clinical picture and the usual cardiac-circulatory observations made during the operation generally give no indication of such disturbances. Additional parameters such as the electroencephalogram can provide information regarding cerebral function in these cases. Electroencephalographic findings in cerebral anoxia, particularly during open heart surgery, was one of the main topics discussed at the electroencephalogram Colloquium held in Marseilles in 1959.[13] In spite of the advances in diagnosis and the relative certainty of the statistical evidence of the significance of electroencephalogram values made during operations with extracorporeal circulation, there are still difficulties in diagnosis and prognostic uncertainty in some cases. The patients often have an unsatisfactory pathophysiological explanation of past or present processes. These studies, begun in 1965, were designed to provide a critical evaluation of the prognostic significance of the electroencephalogram in special cases during and after cardiac surgery.

Methods

Pre- and postoperative electroencephalogram measurements were made with a large 12 or 16-channel machine under standard conditions (Time constant 0.3 sec; filter 70 Hz; speed 3 cm/sec, amplification 50 μV = lcm or 100 μV = lcm) with various uni- and bipolar programs. Two channels of a monitoring unit (time constant 0.3 sec; filter 50 Hz; paper speed 5 cm/sec, amplification 100 μV = lcm) were available for intraoperative examinations. For particular problems, an additional mobile 16-channel apparatus was employed.

Taking into account the narcosis, the electroencephalogram findings were compared with the clinical course, psychoneurological status, blood gas analyses and arterial and venous pressure.

The following values for circulatory function and blood gas analysis were considered pathological: drop in blood pressure under bypass conditions of below 50 mm Hg for longer than five minutes, increase in the central venous pressure over 25 mm Hg for longer than 10 minutes, repeated increases in venous pressure even if they lasted only for a short time, increase in venous pressure over 25 mm Hg with simultaneous fall in blood pressure to values below 50 mm Hg, increase in pCO_2 over 60 mm Hg, drop in pCO_2 below 30 mm Hg, increase in pH to 7.50 or drop in pH below 7.25.

Five hundred and seventy-four cardiac operations (377 closed and 197 open) were carried out in the Surgical Department of the University of Giessen during a three-year period.

Electroencephalogram was performed primarily in patients with a congenital heart defect or requiring valve replacement in whom operation necessitated extracorporeal circulation. It was also carried out in patients with mitral stenosis.

The evaluation of a total of 234 preoperative and 82 postoperative measurements as well as 192 intraoperative controls served as the basis for the present study.

Results

Although 90% of the preoperative measurements could be regarded as normal or slightly irregular, more than 60% of the patients were found to have general changes in the electroencephalogram values of varying degrees postoperatively. Thus the number of normal or slightly changed values dropped to below 40% (Table 1). Disturbed rhythm was distributed

TABLE 1

Electroencephalographic Findings in Pre- and Postoperative Examinations.

Type of Electroencephalogram finding	Preoperative No.	%	Postoperative No.	%
Total Number	243	100.0	82	100.0
Normal	61	25.1	12	14.6
Somewhat irregular/irregular	158	65.0	20	24.4
Generalized changes	24	9.9	38	46.4
Iso-electric Electroencephalogram	—	—	12	14.6
Dysrhythmia	16	6.6	6	7.3
Focal finding	17	7.1	25	30.5

*From the Neurosurgical Department (Director: Prof. H. W. Pia) and the Surgical Department of the University of Giessen (Director: Prof. K. Vossschulte).

equally among the pre- and postoperative measurements. The number of focal disturbances rose from 7.1% preoperatively to 30.5% postoperatively.

Only the basic rhythm could be evaluated intraoperatively because of the 2-channel lead with fronto-occipital placing of the electrodes. The determination of focal changes requires a denser electrode placing. Pathological curves were found in 60.7% of the intraoperative electroencephalogram measurements. Constant slowing of the electroencephalogram pattern, varying from slight to marked, was found in 5.2% of the patients. Slowing dominated in 14.1% of the patients before the introduction of the bypass, in 44.8% during the bypass and in 3.6% after bypass (Table 2). Severe slowing of the basic rhythm was found in 18.4% of patients in these phases, and severe irreversible changes in the electroencephalogram appeared in 12 (6.3%).

After Bypass

Good correlation between the pathological haemodynamic and blood gas values and electroencephalogram findings is observed only after bypass, whereas before and during bypass the haemodynamic and blood gas changes are minimal (Table 3). Only 27.1% of the patients showed pathological haemodynamic values and 11.5% pathological blood gas analyses.

Neurologic-Psychological

Neurological or psychological dysfunction was recognisable in 26 patients (13.5%) postoperatively. Nine of them had slight transitional symptoms of a psychological character or only increase in psychomotor restlessness; the rest showed severe dysfunction, including deep cerebral coma or decerebration in 10.

Seizures

Seizures occurred in six cases (Table 4). Three of the patients showed no abnormalities during the intraoperative electroencephalogram control, whereas the majority had a slowing of the basic rhythm before or during the bypass.

Discussion

Cyanotic Heart Disease

Slight changes in the electroencephalogram picture are found in many patients with cardiopulmonary diseases, although only a fraction of these show subjective or objective signs.[23] The electroencephalogram is more often pathologi-

TABLE 2
Electroencephalographic Changes During Cardiac Operations.

				Non-pathological		Pathological	
		No.	%	No.	%	No.	%
No pathological Electroencephalogram changes	Slower rhythm	12	6.2				
	Faster rhythm	15	7.8				
	Somewhat irregular	28	15.1				
	Irregular	6	3.0				
				62			
Constant Electroencephalogram changes	Slight	6	3.0				
	Moderate	3	1.7				
	Severe	1	0.5				
						10	5.2
Slowing before bypass	Slight	5	2.6				
	Severe	22	11.5				
						27	14.1
Slowing during bypass	Slight	42	21.9				
	Moderate	35	18.2				
	Severe	9	4.7				
						86	44.8
Slowing after bypass	Moderate	4	2.1				
	Severe	3	1.7				
						7	3.6
		192	100.0	62	32.3	130	67.7

cal in patients with cyanotic heart defects.[5,12,19] In the patients studied here, some 10% showed slight or moderate slowing of the basic rhythm, whereas 13.7% had dysrhythmia or focal disturbances. A relationship between these preoperative findings and possible intraoperative deterioration or pathological postoperative values could not be proved. Patients with dysrhythmia or focal electroencephalogram findings showed no changes either intraoperatively or postoperatively when the electroencephalogram curves were compared. A tendency to regulation was found in two patients after operation who had shown generalised electroencephalogram changes preoperatively. This can be attributed to improvement in the cerebral blood supply. Thus the preoperative electroencephalogram picture gives no indication of the prognosis but is of value as an indicator for the severity of the cardiac disease as related to chronic impairment of the cerebral blood circulation.[3,5,12]

Basic Rhythm

In general, the effect of narcosis can be ignored when evaluating the intraoperative electroencephalogram findings as the narcosis is generally superficial, and slowing of the basic rhythm occurs within the fast intermediate waves or the alpha-band.[16] Activation of the basic rhythm or increase in the basic frequence can indicate increased arousal-function.[6] However, even during deep narcosis or hypothermia, sudden changes in the basic rhythm must indicate a momentary change in the excitation level.[6,7,13,14,29,30,32] During the operation, the electroencephalogram was normal or could not be regarded as pathological in only one third of the patients. One out of 20 showed a constant slowing of the basic rhythm which could not be correlated with the pre- or postoperative electroencephalogram values, either as to onset or cause. Decerebration rigidity occurred in one patient postoperatively. In almost two thirds of the patients, however, mild (24.5%),

TABLE 3

Haemodynamic and Blood Gas Analysis Changes During Operation in Relation to the Electroencephalogram Changes.

Electroencephalogram Finding		No of Patients	Without Changes		Haemodynamic Changes		Blood Gas Analysis Changes		Total Number Pathological Changes	
			No.	%	No.	%	No.	%	No.	%
No pathological finding		62	46	74.1	12	19.4	4	6.5	16	25.0
Constant Electroencephalogram changes		10	9	90.0	1	10.0	—	—	1	10.0
Electroencephalogram changes	Before bypass	27	15	55.6	6	22.2	6	22.2	12	44.4
	During bypass	86	48	55.8	28	32.6	10	11.6	38	44.2
	After bypass	7	—	—	5	71.5	2	28.5	7	100.0
Total		192	118	61.4	52	27.1	22	11.5	74	38.6

TABLE 4

Intraoperative Electroencephalogram Finding in Patients with Postoperative Neurological-Psychological Dysfunction

Type of Postoperative Dysfunction	No Pathological Changes	Constant Electroencephalogram Changes	Slowing of Electroencephalogram			Total
			Before Bypass	During Bypass	After Bypass	
Decerebration/Coma	1	1	2	5	1	10
Psychosis	—	—	1	2	1	4
Psychomotor unrest	2	—	1	2	—	5
Focal cerebral dysfunction	—	—	1	—	—	1
Seizures	—	—	1	5	—	6
Total	3	1	6	14	2	26

moderate (20.3%) or severe slowing (17.9%) appeared during the operation although the basic rhythm at the start was within normal limits.

Blood Gas Values

The changes in electroencephalogram which occur during the first operative stage are generally due to mild hyperventilation with alkalosis.[9,15] There is probably increased breakdown of acetylcholine under hyperventilation, which would also explain the increase in pulse rate often found. In general, however, the changes in blood gas values during operation do not yield any specific information.[15,16] A sudden decrease in amplitude can be due to a metabolic acidosis.[7] Out of 192 patients, only 22 (11.5%) showed pathological blood gas values and one fifth of these had no electroencephalogram changes. In the other patients, there was no definite correlation between the change in blood gas values on either the acid or alkaline side and the slowing or flattening of the electroencephalogram waves. This is due to the fact that simultaneous but not marked haemodynamic changes were present. Thus the electroencephalogram finding is chiefly the expression of a primary circulatory disturbance.

Haemodynamic Values

Pathological haemodynamic values were found in four patients during operation. But even here, the haemodynamic changes were similar both in the 20% of the patients who had normal control electroencephalogram values and in the 30% who showed a slowing of the electroencephalogram during operation. According to various authors, venous pressure is significant.[16,24,27,21,30] Prolonged *increase in venous pressure* can lead to the formation of cerebral oedema. A slow *fall in arterial pressure* of up to 35 mm Hg is tolerated by the brain without measurable change in activity.[18,32] A sudden drop, however, leads to a marked slowing and particularly flattening of the electroencephalogram as stressed by Arfel[1] (1961 and 1967), Kubicki (1960) and Silverstein (1960). Both a drop in arterial pressure and prolonged rise in venous pressure lead to an inadequate oxygen supply, i.e., hypoxia as Davis and Davis[9,10] pointed out as early as 1939.

Hypoxia

Hypoxia acts primarily on non-specific systems such as reticular formation. Damage to the sensory or motor systems is secondary.[11]

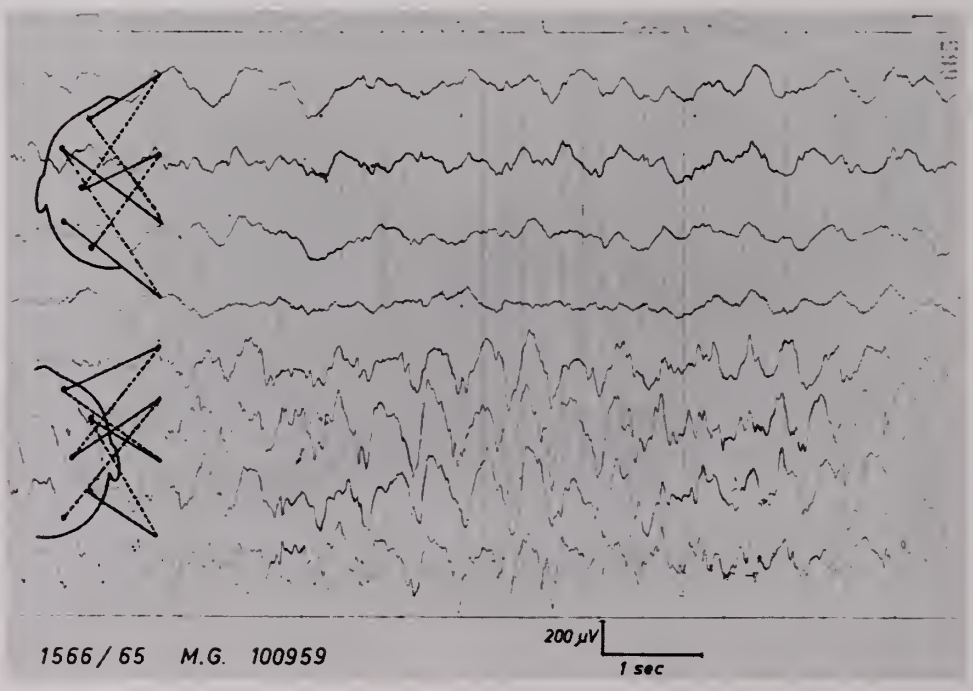


Fig. 1—A left-sided tonoclonic convulsion occurring immediately after operation with electrocardiogram during the awakening phase. Moderate to severe generalised changes in the electroencephalogram. Convulsive activity in the region of the right hemisphere.

If there is prolonged or irreversible slowing of the basic rhythm during operation, then recognisable cerebral dysfunction must be expected postoperatively.[26,30] Twelve patients with irreversible intraoperative electroencephalogram changes showed focal defects of a neurological or psychological character postoperatively. The significance of seizure potentials as a measure of the degree of acute hypoxic damage to the cerebral cortex which is sometimes stressed[4] is secondary to the other electroencephalogram changes.

Meyer et al.[22] proved that if the onset of anoxia or hypoxia is sudden, convulsions can appear clinically although no seizure potentials are recognisable in the electroencephalogram. No cramp potentials were observed in any of the patients in this study during operation, although cerebral convulsions occurred in two patients in the immediate postoperative phase (Figure 1) and in four patients somewhat later. Thus, in general, seizure potentials cannot be regarded as a measure of the degree of hypoxia. In animal experiments it has been shown that there is a limited flattening of the electroencephalogram pattern over the area of infarction following an embolism.[2,25]

Such detailed observations were not possible

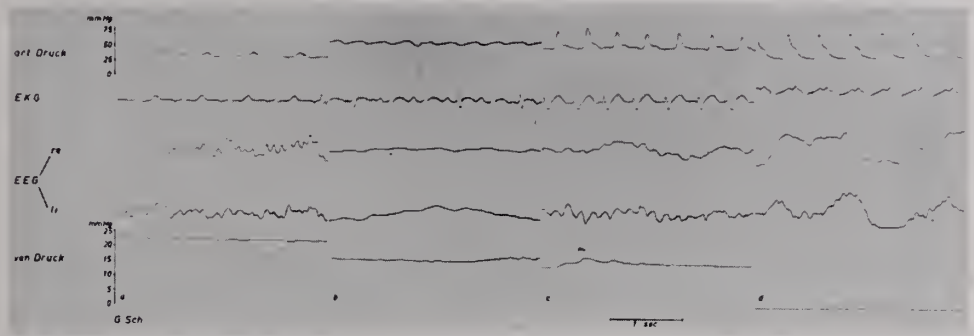


Fig. 2—(a) Slight slowing of the basic rhythm during increased venous and low arterial pressure at the commencement of the bypass. (b) In spite of improvement in the pressure values before end of the bypass, a severe flattening and slowing of the electroencephalogram occurred which (c) subsided after five minutes. The slowing was still marked over the right hemisphere. (d) At the end of the operation, moderate to severe general changes particularly on the right. Postoperative decerebration.

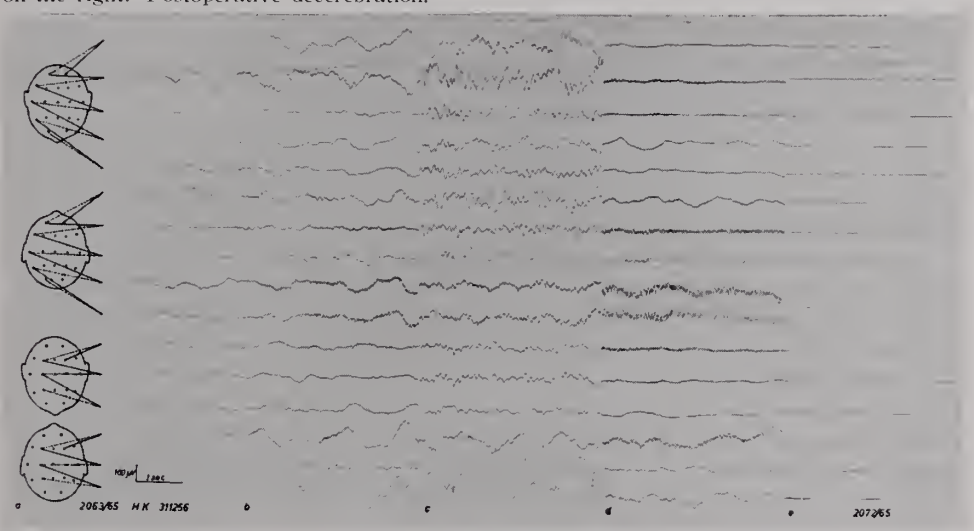


Fig. 3—(a) 12.30 at the end of the operation, patient comatose without reactions or reflexes. Severe generalised electroencephalogram changes particularly on the right side. (b) 1340 significant increase in muscle tone and in the basic rhythm particularly over the left hemisphere in the sense of a moderate to severe general change. (c) 13.50 generalised tonoclonic convulsion. Electroencephalogram shows moderate generalised change with epileptic activity particularly over the right hemisphere. (d) Onset of reflex extension particularly on the left side. Electroencephalogram again shows generalised change particularly on the right side. (e) 9.20 of the first postoperative day. Deep coma, complete loss of reaction and reflex activity, atonia, respiratory paralysis, no temperature regulation. Base line electroencephalogram even at high sensitivity.

in the operating theatre where there was only a 2-channel, fronto-occipital or frontoparietal monitor available. Even an electroencephalogram apparatus with four channels does not yield more information in this respect. Such data can be obtained only with a larger electroencephalogram apparatus and denser placing of the electrodes, using perhaps an international standard. A flattening of the curves in the monitor electroencephalogram can be due to general hypoxia, acidosis or embolism. For anatomical reasons, small air emboli affect the right side primarily.[2,25] Air emboli were suspected in two patients (Figure 2) and such complications were assumed in others on the basis of the electroencephalogram changes (Figure 3).

Compensatory Ability

The fact that there can be marked electroencephalogram changes during the operation while postoperatively there are no neurological or

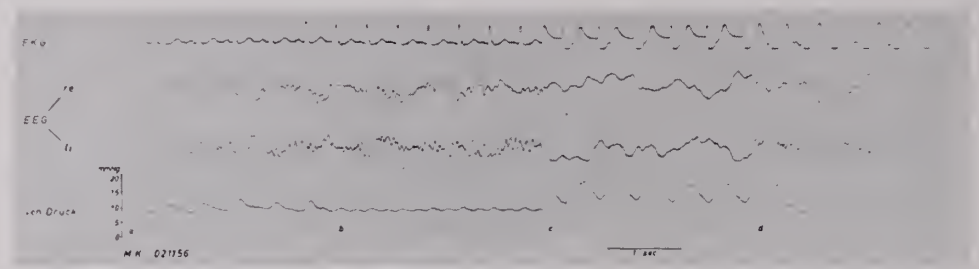


Fig. 4—(a) Insignificant basic rhythm of an 11-year-old child before bypass. (b) Slight increase in irregular intermediate waves during fall in arterial pressure. (c) Severe slowing on increase in venous pressure during bypass. (d) Quickening of basic rhythm on return of pressure to normal. Patient neurologically and psychologically normal postoperatively.

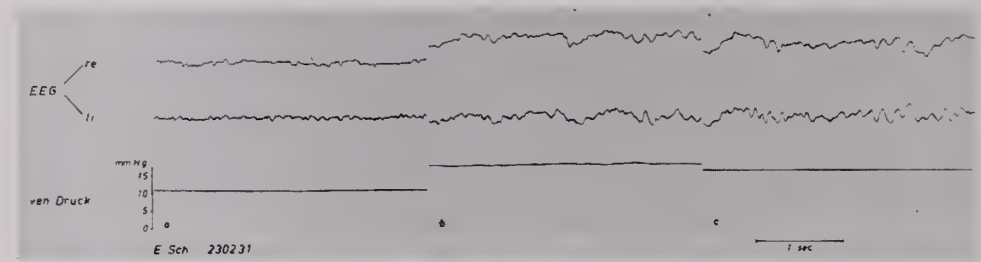


Fig. 5—(a) Unremarkable electroencephalogrim at beginning of monitoring. (b) Slowing of basic rhythm, right more than left on total bypass. (c) Changes extend beyond operation. Postoperative decerebration.

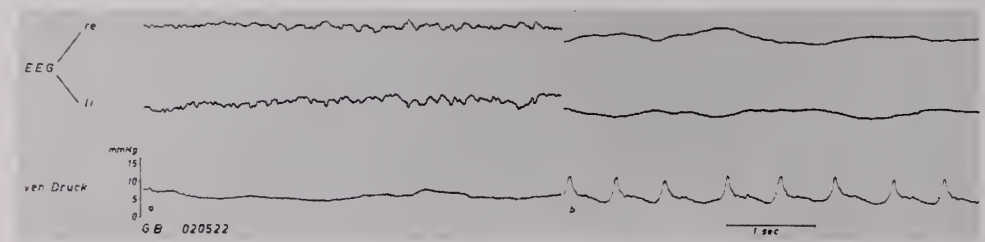


Fig. 6—(a) Moderately severe generalised changes before bypass with unremarkable narcosis. (b) Increased flattening and slowing into the sub-delta region under bypass.

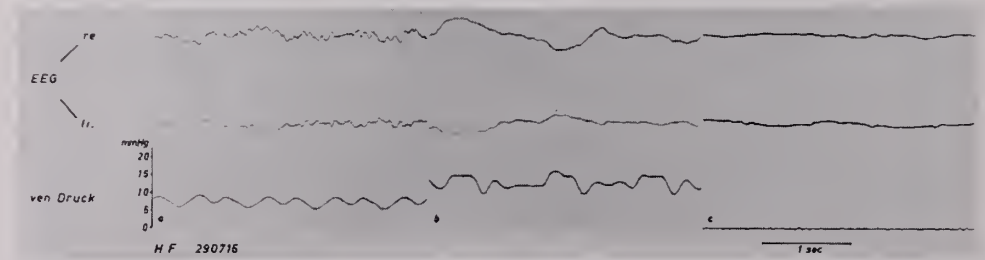


Fig. 7—(a) Basic rhythm of the electroencephalogram in the alpha region before bypass. (b) Severe slowing of the basic rhythm at the end of the operation in which there were marked and prolonged changes in the arterial and venous pressure during bypass. (c) Transition into flat base line fluctuations with loss of reaction and reflexes, atonia and coma.

psychological signs is probably due primarily to the compensating ability of the cerebral blood circulation or cerebral metabolism (Figure 4). In many cases, neither narcosis, operation nor unremarkable control values can explain the intraoperative electroencephalogram findings or the postoperative impairment (Figures 5, 6). The most noticeable factor is that marked electroencephalogram changes can often be observed as early as the start of the bypass (Figure 7). This can possibly be explained by assuming a poor ability for compensation during the change in circulation necessary for the operation.

Postoperative electroencephalogram measurements show a significant increase in gen-

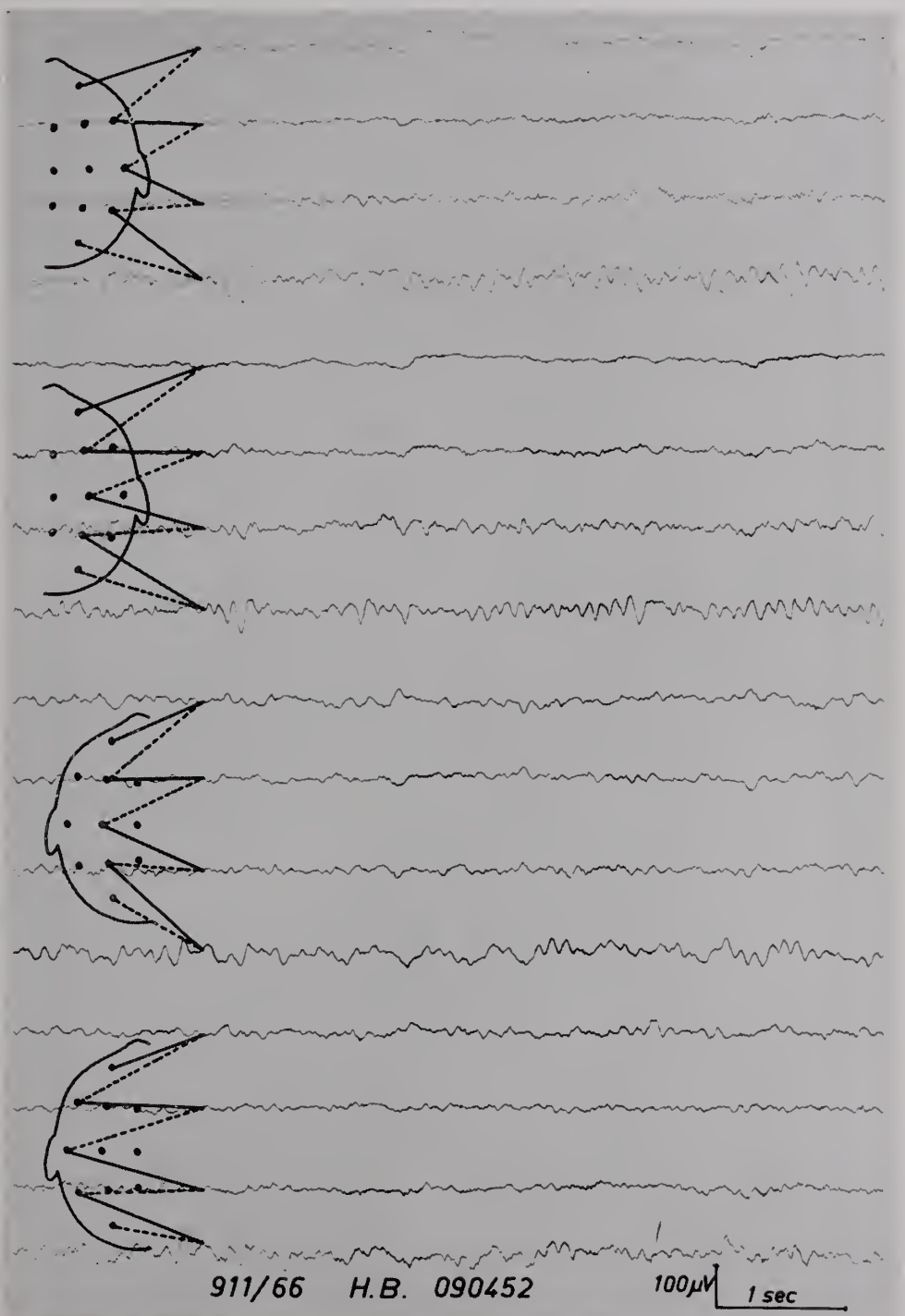


Fig. 8—Proof of a left occipitotemporal focus in the postoperative electroencephalogram.

eral and focal slowing (Figure 8). A corresponding clinical-neurological dysfunction was found in only one patient with a postoperative focal abnormality in the electroencephalogram. In the majority of patients, the symptoms were general, such as increased motor unrest or temporary mild delirium. Since there was no definite clinical indication of a cerebral embolism, the increase in focal electroencephalogram changes can be explained only by assuming a limited cerebrovascular insufficiency due to previous damage. A so-called base line electroencephalogram[20] was found in 12 patients. In seven of these, the base line electroencephalogram was found intraoperatively and all died immediately after operation. Although only three of the patients with postoperative neurological or psychological dysfunction showed no abnormality of the electroencephalogram pattern during the operation, all showed localised or general changes in the postoperative electroencephalogram control. In this respect, one can agree with Storm Van Leeuwen[30] that electroencephalogram changes appeared when "something had gone wrong."

Thus from the point of view of this study, it can be stated that the electroencephalogram is one index among other clinical and biological findings and is not significant when considered alone.

Summary

The evaluation of 243 preoperative, 192 intraoperative and 82 postoperative electroencephalograms in conjunction with the clinical-neurological findings and the pathological haemodynamic and blood gas analysis values determined intraoperatively has shown the following: disturbances in the electroencephalographic function in heart diseases or during cardiac operations are almost entirely due to localised or generalised hypoxy- or anoxydosis.

Localised hypoxydosis can arise after *embolitic processes* (thrombi, chalk particles) or by *lowering of the systemic blood pressure* which causes cerebrovascular insufficiency in the previously damaged areas. In general, they can be detected only by a dense placing of the electrodes and thus usually escape detection with the 2-channel monitor used during the operation. Air and silicon emboli are intermediate in this respect as the particles are larger and more numerous and give rise to multiple emboli. Most of the cerebral dysfunctions appearing intraoperatively are due to acute or chronic generalised arterial hypoxydosis and only a few to venous hypoxydosis. In agreement with other authors, the blood gas changes were found to be insignificant.

The electroencephalogram changes during cardiac operations took the form of a slowing or flattening of the basic rhythm. Good correlation between the intraoperative electroencephalogram changes and the postoperative findings was observed only when there was marked irreversible slowing of the electroencephalogram pattern. The preoperative electroencephalogram was found to be of no significance for the course during and after operation but was an indication of general or localised cerebral dysfunction which was not clinically manifest. Pathological haemodynamic and blood gas values explained the electroencephalogram findings in only one third of the patients. A slowing or flattening of the basic rhythm during operation was observed in patients with normal postoperative neurological or psychological findings. These observations support the idea of compensation or load capacity of the organism. Neurological or psychological dysfunction occurred in 13.5% of the patients postoperatively. One out of eight had a normal electroencephalogram during operation. However, complications occurring between the end of the operation and observation on the ward could not be excluded in these cases.

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May you live all the days of your life.—Jonathan Swift

Formation of New Bone in Diffusion Chambers

H. ECKE, M.D.* and G. SKIBBE, M.D.*

Organ transplantation and the immunological problems connected with it are arousing increasing interest. Processes similar to those observed in organ transplantation are also found in skin grafts and implanted bone chips.

The actual founder of the so-called osteoblast theory was Bernhard Heine in 1836. The Frenchman Ollier[1] showed that autografts of bone healed if they were covered with periosteum, whereas those without periosteum became necrotic. At the beginning of this century, Marchand[2] and Barth proved that grafts which are free of periosteum can survive. Lexer, and also the elder Axhausen and his school, have been the main exponents of the osteoblast theory in this century. In 1912, the Russians Baschkirzew and Petrow[3] broke away from the osteoblast theory and spoke of a chemical affinity which develops the graft and stimulates bone formation. The German surgeon August Bier maintained in 1923 that bone can be formed from bone and can appear as a result of metaplasia whereby hormonal stimulation from the marrow cavity is the prime stimulating factor.

One of the most important supporters of the metaplasia theory was Levander.[4] In 1934 he was of the opinion that free grafted autologous bone fragments die completely after transplantation. This is surprising, as the cells of an autologous skin graft transplanted at the same time survive. New insight into the survival and growth of transplanted bone was provided by the grafting experiments of Goldhaber[5] in 1958. He was able to show without doubt that isologous bone enclosed in a diffusion chamber not only does not die but can also grow. The method of implantation of bone chips in diffusion chambers made of millipore or polyvinylchloride has been developed by Ecke[6] into a quantitative method for the study of bone regeneration. The chambers have such fine pores that nucleated cells cannot pass through the walls although the humoral connection including the passage of macroglobulins is undisturbed. In this way the growth potential of chips of epiphyseal cartilage from growing animals can be quantitatively determined. In a few experiments directed towards determining the regenerative ability of the epiphyseal cartilage using isologous and homologous chips, it was thought that the homologous grafts† show less bone growth than the isologous grafts.† The round cells which prepare the rejection reaction cannot pass through the walls of the diffusion chamber; therefore humoral antibodies must also be active in addition to the cell-bound transplantation immunity. This problem was the basis of the following experiments.

Material and Methods

Thirty-five male rats of the pure strain Wistar W-64 were used as experimental animals. Inbred rats of the strain Sprague-Dawley-68 were used as donors of the homologous bone. Each strain can be regarded as pure, and skin grafting is tolerated between animals of the same strain.

Bone from the ribs was chosen for the first time in these experiments in order to obtain grafts of similar weight. In addition, these bones had no sharp edges which could damage the walls of the chambers. However, they do not show such good osteogenic properties as spongeous bone, because the surface of the graft consists of broad layers of compact bone. The bone fragments were enclosed in the polyvinyl diffusion chambers developed by the authors and were then sealed with thermotongs. The chambers had been previously sterilised by gamma radiation and were considerably less fragile than

*From the Surgical Department of the University of Giessen (Director: Prof. K. Vossschulte).

†See Test Your Word Score, page 1131.

those used in previous experiments which had been sterilised by gas. The finished chambers were planted into pockets on the backs of the rats. Half of the animals were killed after eight weeks and the other half after 16 weeks. The grafts could be retrieved by removing the skin from the back of the rat. The initial weight of the bone chips was compared with that found at the end of the experiment. The weights were obtained with an analytical balance. As found in previous experiments, almost all of the grafts showed an increase in weight due to the formation of new bone (Figures 1 and 2).

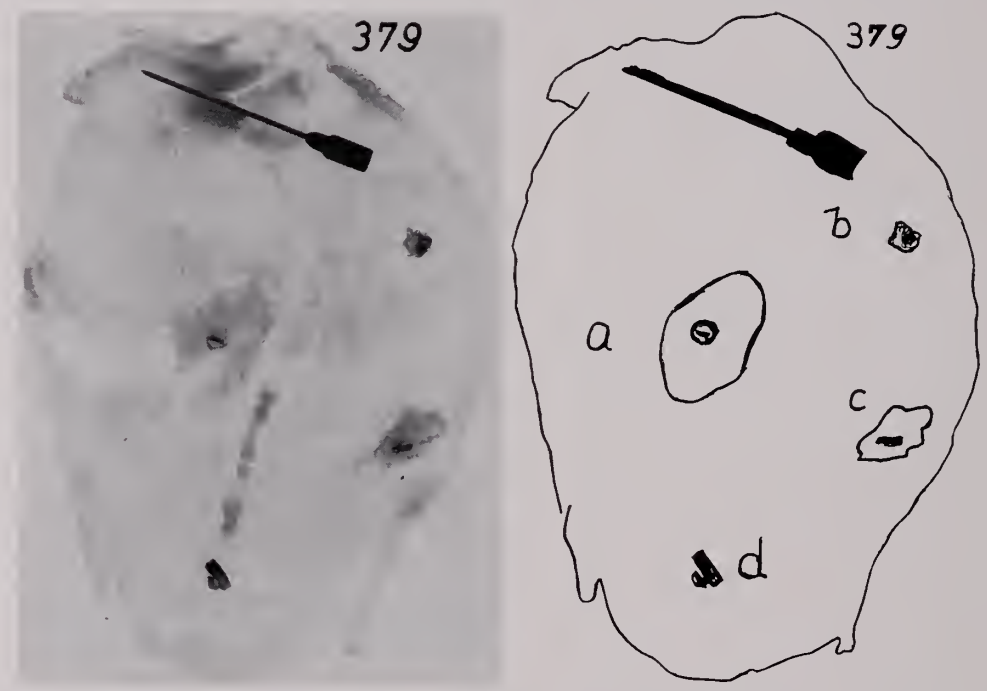


Fig. 1—Radiograph of a rat hide with two implanted bone chips in millipore diffusion chambers. At position *a* there is homologous bone and at position *c* isologous bone eight weeks after grafting. Chamber *c* could not be evaluated as it was not firmly sealed. At position *b* there is homologous and at position *d* isologous bone which has been grafted directly into the skin. The isologous bone *d* shows a definite osteophyte. In chamber *a* recognisable formation of new bone has taken place as seen by the dark halo in its vicinity. The details of this tissue can be seen in Figure 2.

Results

With very few exceptions, the bony substance in the isologous and homologous grafts showed a measurable increase in weight after eight or 16 weeks.

Isologous Grafts

The arithmetic mean of the multiple of the initial weight of the isologous grafts was 1.84 after eight weeks' exposure and 2.05 after 16 weeks. When examined statistically, this difference was not significant, with a degree of error of 5%. In other words, the growth of bone does not increase measurably after eight weeks. This may be due to the fact that, with time, more connective and scar tissue is formed around the chamber so that diffusion is hindered.

Homologous Grafts

In the case of the homologous bone chips, the arithmetic mean of the multiple of the initial weight was 1.78 after eight weeks and only 1.64 after 16 weeks. To be certain that there was no bone destruction, this group was also examined statistically and again no significant difference was found between the two values. Therefore the weight of the homologous grafts also remains the same as that reached after eight weeks' exposure. Finally, the isologous and homologous grafts were compared statistically after eight weeks. No significant difference in weight between the two groups was found. The same result was found after 16 weeks' exposure.

Discussion

Seventy bone grafts in diffusion chambers

were examined; half of them were isologous and the other half homologous grafts. Both groups showed the same increase in weight. This implies that, in diffusion chambers, the same bone growth takes place after transplantation regardless of whether the graft is isologous or homologous and that there is no significant difference in new bone formation between the two types of graft. In the case of homologous bone, therefore, no limiting humoral factor could be demonstrated apart from the cell-bound immunity. These quantitative experiments have also shown that new bone formation is complete within eight weeks in diffusion chambers and no measurable increase can be detected after this period even if the exposure time is considerably longer. This result is important for planning the length of experiments using diffusion chambers.

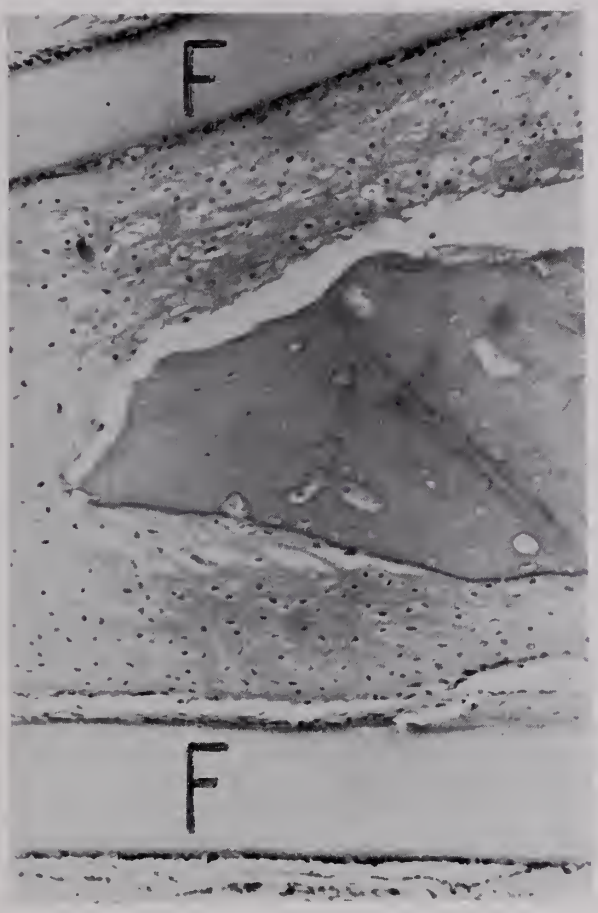


Fig. 2—This shows the microscopic tissue processes in a chamber containing a homologous graft (position *a*, Figure 1). Marginal osteoblasts of the graft have initiated and stimulated the new bone formation in the chamber, the fine porous wall of which is marked *F*. Formation of connective tissue can be seen only in a few sections cut directly through the wall of the chamber. The majority of the osteoblasts in the centre of the graft have died.

Summary

Seventy isologous and homologous bone grafts which had been planted in diffusion chambers on the backs of 35 rats were examined for bone regeneration and the length of time required for new bone formation. It was shown that the homologous grafts, when exposed in diffusion chambers which have humoral connections but are impenetrable for the host cells, show the same increase in weight as the isologous grafts. The main increase in weight takes place in about eight weeks. If one doubles this time period, there is no further significant increase. This may be due to the marked formation of connective tissue in the region of the outer walls of the chamber.

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The world is full of willing people; some willing to work, the rest willing to let them.—Robert Frost

You like not anything new unless you be yourself the author thereof.—Sumner, Lincoln's cabinet.

Historic Hospitals

German Medicine at Johns Hopkins



An octagon ward at the Johns Hopkins Hospital, 1890, a forerunner of today's circular or "silo" floor plan. Courtesy of National Library of Medicine, Bethesda, Maryland.

When Johns Hopkins, the wealthiest man in Baltimore, bequeathed his fortune for the founding of a university and a hospital, he provided for the best of buildings and equipment and for the best men obtainable. It is no accident that of the professors appointed to the new medical school, all but one had studied extensively in Germany. For in the late nineteenth century German medicine was unquestionably the world's best. Virchow had recently developed the new science of cellular pathology, and Koch had laid the foundations of clinical bacteriology. The rapid expansion of scientific activity extended to all branches of medicine throughout Germany.

The newly-appointed faculty of the Johns Hopkins University Medical School set out to transplant the German vigor and expertise to the North American continent. Osler began to build "a great clinic on Teutonic lines, not on those previously followed here and in England, but on lines which have proved so successful on the Continent and which have placed the scientific medicine of Germany in the forefront of the world."

The new medical school opened its doors in 1893 with entrance requirements of a bachelor's degree, a good reading knowledge of German, and prescribed courses in the natural sciences. It introduced the senior students into the wards as integral parts of the hospital team. Perhaps the greatest innovation of all was the development of the residency system of post-graduate medical education.

The hospital, too, was outstanding and innovative. It opened in 1889 with a capacity of 220 beds. Its intimate relationship with the medical school and its pavilion system of architecture with all buildings connected by covered corridors stirred the imaginations of the day.

By the turn of the century Johns Hopkins was providing the same kind of medical leadership in America that Germany was providing to the world.

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The Surgical Prophylaxis of Pulmonary Embolism

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Ligature of the femoral veins has been shown to be useless in the surgical prevention of pulmonary embolism and is no longer used today. The operation can cause considerable impairment of venous drainage from the lower extremities and does not provide efficient protection from thrombi originating in the pelvic veins.

Two other methods of treatment have been used increasingly in recent years: thrombectomy and partial or total ligature of the inferior vena cava.

Thrombectomy

Thrombectomy has become popular for the treatment of fresh pelvic or leg vein thrombosis when fibrinolytic therapy has failed, particularly since the introduction of the ring stripper and Fogarty catheter. This method is also very useful in the treatment of massive venous thrombosis of the lower extremities, phlegmasia coerulea dolens.

Ligature of Inferior Vena Cava

Ligature of the inferior vena cava below the point of entry of the renal veins was designated as a "legitimate operation" by Kocher.[17] In 1911, Trendelenburg[40] used the method successfully in a patient with puerperal pyaemia. Ten years later at the 45th Congress of the German Surgical Society, Martens[21] recommended the technique as a routine operation to shut off the thrombosed veins in thrombophlebitic puerperal pyaemia. However, the method did not become established and was more or less forgotten until revived by Homans (1944) as a method of preventing the dispersion of thrombi. In the last ten years, the partial or complete ligature of the inferior vena cava above the bifurcation has found increasing support, particularly among American surgeons.

Indications for Ligation of the Vena Cava

Among the *indications* for which surgery of the inferior vena cava appears to be advisable as a prophylaxis for pulmonary embolism, the following are recommended in the literature.[2,5,8,24,28,41,43,45]

Micro-embolism

Recurrent pulmonary micro-embolism when anticoagulant therapy has failed and thromboses of the thigh and pelvic veins have been demonstrated. Ligature of the inferior vena cava is mainly indicated in patients with small, more or less symptom-free pulmonary emboli causing increased pulmonary pressure as determined by cardiac catheterisation which cannot be reduced with anticoagulant therapy.

Anticoagulant Therapy Contraindicated

Treatment of pulmonary embolism when thrombolytic or anticoagulant therapy is contraindicated. Patients in this category appear to be particularly susceptible to thrombo-embolitic complications.[9]

Recurrent Embolism

It is widely considered that an operation on the inferior vena cava is indicated in recurrent pulmonary embolism during optimal anticoagulation therapy.

Thrombosis of Pelvic Veins

In septic thrombosis of the pelvic veins, ligature of the inferior vena cava prevents further dissemination of the infected thrombotic material and the resulting effects which are often deleterious.

*From the Surgical Department of the University of Giessen (Director: Prof. K. Vossschulte).

After Pulmonary Embolectomy

After successful pulmonary embolectomy, the operation is of value in avoiding recurrent embolism.

Procedures

Ligation of the inferior vena cava should be avoided in patients over 80 years of age and in those with advanced incurable malignancies.

The best approach to the inferior vena cava both in partial and total occlusion is a right-sided, extraperitoneal procedure using a flank or high gridiron incision. The intraperitoneal approach is used only when simultaneous ligation of the ovarial veins is also necessary, for example in thrombosis of the pelvic veins. Preparation of the inferior vena cava between the bifurcation and point of entry of the renal veins presents no technical difficulties. The vein is freed bluntly with the help of a bent Overholt clamp and ligated with a thick silk thread. Others recommend transection of the inferior vena cava.

The authors who support partial occlusion stress that this relatively small operation is sufficient to prevent the appearance of further pulmonary emboli and, in contrast to total ligature, does not inhibit venous back flow.[2,8,10,23,25,28,43]

Suture Filter

De Weese and Hunter[7] suggest the formation of a suture filter lying tangentially in the inferior vena cava. This is made using a continuous mattress suture with 2-3 mm between the threads situated in the vascular cavity. This method has found little support, however, as it is time-consuming and not always technically feasible.

Plication

The plication method of Adams and De Weese,[7] on the contrary, has found rapid support. The teflon clip, which is some 2 mm thick and 35 mm long, has several U-shaped openings, each with a diameter of 4 mm. There is a narrow gap between the teeth of the upper part and the smooth lower part which prevents pressure necrosis when the clip is closed. After fixation of the two parts of the clip, the inferior vena cava is subdivided by ligature into four channels, each 3 mm in diameter, which prevent the passage of a thrombus of greater diameter.

In the plication technique recommended by Spencer,[35] three to four mattress sutures are made at distances of 4-5 mm after temporary occlusion of the inferior vena cava. By adapting the anterior and posterior walls of the vessel, channels are formed in the lumen, each some 3 mm in diameter. Silk is used for suturing.

Ravitsch[32] plicated the vessel with a Russian suture apparatus. This modification is attractive because of its rapidity.

Teflon Clip

The teflon clip designed by Moretz[24] is so constructed that a gap 3 mm broad remains in the vessel after closure.

Porcelain Spheres

Mozes[25] and co-workers use four porcelain spheres of 4 mm diameter, through which a silk thread is passed. On tightening the thread, the lumen is subdivided into four small tunnels.

Complications

A syndrome characterised by severe *hypotension* and *oliguria* occurs occasionally as an early complication following total ligature due to decrease in the back flow. Death due to acute *renal failure* has been described.[14] Severe *acute thrombosis of the ileo-femoral* vein is another early complication which can occur after partial or total ligature in the first postoperative days. Spencer[35,36,37] controlled this complication which occurred in four out of 39 patients by immediate thrombectomy.

Small recurrent pulmonary emboli have been reported in the early postoperative phase, usually after partial but also after total ligature of the inferior vena cava. The emboli usually originate in the larger collateral veins, particularly the ovarian veins, and occasionally at the point of plication or immediately proximal to these areas.[5,8,24,25,28,37]

Supporters of transection of the inferior vena cava point out that ligature alone leaves a blind sack between the entry of the renal veins and the point of ligation which is under tension. This is presumed to encourage thrombus for-

mation. De Takats recommended the simultaneous ligature of the ovarian veins.

Mortality

The operative mortality (4-18%) is the same after total or partial ligature of the vena cava. The majority of the deaths were not related to the operation but were due to the basic disease.[5,23,25,37]

Results

Besides numerous favourable reports of normal circulatory conditions, there are also those describing unfavourable consequences varying from oedema of the leg and pain over the varices to more or less marked thrombotic disturbances, such as dermatitides* and ulcers.

Congestion

Menendez,[22] Ochsner,[26,27,28,29] Schauble[39] and others have shown that persistent symptoms of congestion appear only if the iliac or femoral veins are already blocked at the time of ligature. If the venous periphery is healthy, there are generally neither acute nor chronic consequences.

Prolonged Circulation Time

The measurements of venous pressure and circulation times made by Ferris[10] and co-workers after ligature showed that there was only an increase in pressure in the femoral veins and prolonged circulation time in patients with thrombosis below the ligature or in the region of a larger collateral vessel or when a peripheral thrombophlebitis occurred after ligation. Signs of obstruction of venous outflow were found only in this group of patients.

Obstruction of the Outflow

Wheeler[45] and co-workers were able to show that the follow-up results after partial ligature are more favourable than those after total occlusion. In two thirds of the patients (66%) after total occlusion, there were signs of obstruction of the venous outflow which necessitated the wearing of elastic stockings (observation time of 12.5 years). Thirty-four percent had slight symptoms, 28% moderate and 4% severe. A further group of 8% had ulceration. This result is compared with that of another group of patients who underwent plication of the inferior vena cava. During a follow-up of two and a half years, only 20% showed mild oedema of the lower extremities.

By means of venographic studies De Meester and co-workers showed that a total blockage of the vessel at the site of plication occurred in 40% of the patients with partial interruption of the inferior vena cava over an observation period of one month to six years. Bergan[2] reported a value as high as 66%. The most favourable results were found by Spencer[27] and Moretz,[24] who noted total obstruction in only 13 or 14% of their patients.

Giessen Series

Since 1960, six patients have undergone total and one patient partial ligature of the inferior vena cava directly following successful pulmonary embolectomy in the Surgical Department of the University of Giessen. Previously four patients had died during the first three postoperative days after embolectomy; the cause of death was proved by autopsy to have been due to recurrent embolism. Since then, there have been no further cases of the latter.

Temporary Oedema

In three patients, temporary oedema of the leg occurred during the first postoperative days, but subsided rapidly in two of the patients with conservative therapy. In the third case, there was more marked oedema and a congestive dermatitis which required longer treatment.

Mortality

Two patients who underwent successful embolectomy in 1960 and 1962 respectively have since died of their original complaint; the remaining five patients showed no symptoms on examination which could be attributed to congestion of venous outflow. None revealed visible or palpable swelling of the lower extremities. At the time of follow-up, two patients had been operated six years previously; two, four years previously, and one, seven months previously.

*See Test Your Word Score, page 1131.

Collateral Bypass

In three patients, a well-developed collateral bypass over the *prevertebral* plexus was found on phlebography (40 cm of contrast medium Conray 60% was injected bilaterally into the ischial tuberosity). In one patient this was supplemented by a clearly visible connecting route of surface veins in the wall of the thorax and abdomen (Figure 1).



Fig. 1—Contrast picture of the deep pelvic veins. Extensive anastomosis between both internal iliac veins. Outflow of the contrast medium over the prevertebral plexus via the ascending lumbar veins.

The existence of a *cavo-portal* collateral bypass was shown in the fourth patient. There were no signs of obstruction of the venous outflow of the lower extremity in this patient, who had undergone amputation of the left leg in the Second World War (Figure 2). Phlebography was performed in the fifth patient, a 56-year-old woman, seven months after *partial* occlusion of the inferior vena cava with a Moretz clip. It showed a narrowing of the vessel in the region of the teflon clip with rapid, undisturbed outflow in the cranial direction at the point of plication above the meeting point of the iliac veins (Figure 3). The right common iliac vein was well demonstrated, while the left common iliac vein was clearly distended. Their point of entry into the inferior vena cava could not be seen; apparently there was thrombotic obstruction at this junction. Apart from the collateral connection between the two interior iliac veins, no extensive collateral bypass had been devel-

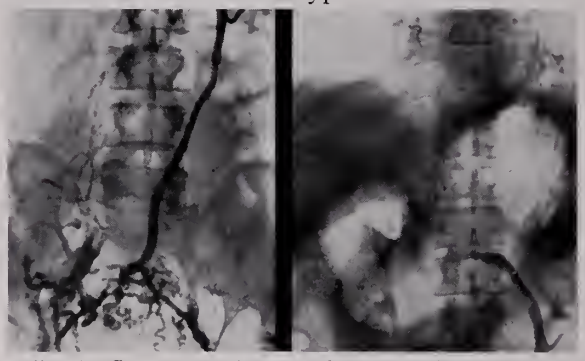


Fig. 2—Cavo-portal bypass after total ligature of the inferior vena cava. Outflow of the contrast medium over a pencil-thick inferior mesenteric vein in the cranial direction (left). Point of entry into the portal veins recognisable in a later picture (right). The inferior vena cava is not visible.



Fig. 3—Cavography seven months after partial occlusion of the inferior vena cava with a MORETZ clip. Point of plication can be seen above the meeting point of the iliac veins. Venous outflow in the direction of the cranium is unimpaired. The left communal iliac vein is clearly distended. Point of entry into the inferior vena cava is blocked by a thrombus. Collateral connection between both internal iliac veins.

oped. This suggests that the inferior vena cava was still sufficiently patent.

Concluding Comments

It remains to be seen whether the partial occlusion of the inferior vena cava gives better results than total ligature. The periods of observation are still too short to lead to a definite conclusion. Total venous occlusion is to be preferred in cases of recurrent pulmonary micro-emboli that have resulted in pulmonary hypertension as well as in septic thrombosis of the pelvic veins. Efficient anticoagulation therapy must be started immediately after the operation on the inferior vena cava in order to prevent exacerbation of a thrombus lying proximal or distal to the occlusion. It is not certain how far a later thrombotic occlusion in the region of the fold can be prevented. Signs of congestion which appear postoperatively in the lower extremities can usually be compensated with elastic stockings and raising the bed end 20 cm.

The operation on the inferior vena cava requires no great expenditure and is relatively simple technically, so that it can be carried out in smaller hospitals. The conservative opinion on occlusion of the inferior vena cava because of fear of complications in the lower extremities does not appear to be justified and should be critically examined, from both the surgical and the medical point of view.

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The Mushroom Crowd

Rapid growth has been compared by a number of people, including some soberspoken scientists, to cancer. The late Dr. Alan Gregg, of the Rockefeller Foundation, speaking to the American Association for the Advancement of Science in December 1954, said: "I suggest, as a way of looking at the population problem, that there are some interesting analogies between the growth of the human population of the world and the increase of cells observable in neoplasms.

"To say that the world has cancer, and that the cancer cell is man, has neither experimental proof nor the validation of predictive accuracy; but I see no reason that instantly forbids such a speculation. If such a concept has any value at the outset, we should quite naturally incline to go further by comparing the other characteristics of new growths with the observable phenomena related to the extraordinary increase now noted in the world's population.

"What are some of the characteristics of new growths? One of the simplest is that they commonly exert *pressure* on adjacent structures and, hence, displace

them. . . . Border warfare, mass migrations, and those wars that are described as being the result of population pressures resemble the pressures exerted by new growths. We actually borrow not only the word pressure but also the word invasion to describe the way in which new growths by direct extension preempt the space occupied by other cells or types of life. The destruction of forests, the annihilation or near extinction of various animals, and the soil erosion consequent to overgrazing illustrate the cancerlike effect that man—in mounting numbers and heedless arrogance—has had on other forms of life on what we call 'our' planet.

"*Metastasis* is the word used to describe another phenomenon of malignant growth in which detached neoplastic cells carried by the lymphatics or the blood vessels lodge at a distance from the primary focus or point of origin and proceed to multiply without direct contact with the tissue or organ from which they came. It is actually difficult to avoid using the word colony in describing this thing physicians call metastasis. Conversely, to what degree can colonization of the Western Hemisphere be thought of as metastasis of the white race?

"Cancerous growths demand food; but, so far as I know, they have never been cured by getting it. Furthermore, although their blood supply is commonly so disordered that persistent bleeding from any body orifice suggests that a new growth is its cause, the organism as a whole often experiences a *loss of weight and strength* and suggests either poisoning or the existence of an inordinate nutritional demand by neoplastic cells—perhaps both. The analogies can be found in our plundered planet—in man's effect on other forms of life. These hardly need elaboration—certainly the ecologists would be prepared to supply examples in plenty of man's inroads upon other forms of life.

"At the center of a new growth, and apparently partly as a result of its inadequate circulation, *necrosis* often sets in—the death and liquidation of the cells that have, as it were, dispensed with order and self-control in their passion to reproduce out of all proportion to their usual number in the organism. How nearly the slums of our great cities resemble the necrosis of tumors raises the whimsical query: Which is the more offensive to decency and beauty, slums or the fetid detritus of a growing tumor?

"One further analogy deserves attention. The individual cells of new growths often show marked *variations of size, shape, and chemical behavior.* This may be compared with the marked inequalities of health, wealth, and function so conspicuous among the human beings in overpopulated countries. Possibly man's invention of caste and social stratification may be viewed in part as a device to rationalize and control these same distressing discrepancies of health, wealth, and status that increase as the population increases.

"If Copernicus helped astronomy by challenging the geocentric interpretation of the universe, might it not help biology to challenge the anthropocentric interpretation of nature?"*

*William Vogt: People! Challenge to Survival, 1960.

DERIVATIVELY SPEAKING

Hadernkrankheit—a rag-picker's disease—from German *Hader* (rag) and *Krankheit* (disease).

Carcinoma of the Breast*

Surgical Treatment of Metastases

H. R. SCHOEN, M.D.†

THE SAME PRINCIPLE applies to the surgical treatment of carcinoma of the breast as to primary malignant tumours of epithelial or connective tissue origin, i.e., the tumour must be removed as radically as possible. However, this is rarely possible in carcinoma of the breast because of the tendency to the formation of multilocular metastases. Metastases of the long bones are ideal for radical operation, but indication for resection or amputation must be carefully considered. Forty to 70% of these patients must be regarded as having micrometastases of the bone, particularly in the spine (80-90%) which cannot be verified clinically.

Extended Metastases

Metastases of carcinoma of the breast located in the abdominal organs, for example, liver or adrenals, usually appear so late clinically that their radical removal is no longer possible.

The majority of the patients referred to the surgeon because of metastases of carcinoma of the breast are suffering from metastases in the bone which have become noticeable because of pain, swelling, paresis and fractures. The diagnosis is not difficult because in most cases the patient has already undergone mastectomy because of a carcinoma of the breast. In all doubtful clinical and radiological changes of bone, particularly spontaneous fractures, the mammary glands of patients of both sexes should be palpated. If the diagnosis of metastasis of a mammary carcinoma is proved, regardless of whether the latter has already been removed or is still present, then immediate surgical treatment must be considered. Radical operation can only rarely be performed because of the reasons mentioned above. The palliative operations are, therefore, of even greater significance. They save the patient from prolonged immobilisation of the extremity with fatal results such as pneumonia, infection of the urinary tract, or decubital ulcers.

Isolated Metastases

Abrams and co-workers found solitary or multiple bone metastases in 27% of 1000 carcinoma patients on post-mortem examination. Approximately two thirds of all autopsied patients with carcinoma of the breast had bone metastases.

Even the extirpation of isolated metastases from the brain and lungs can be performed only if the general condition of the patient is sufficiently good and the presence of other metastases can be excluded with certainty.

Studies by Penzholz (1968) showed that the statistical incidence of intracranial metastases in autopsies was 35%, of which 72% were located in the cerebrum and 21% in the cerebellum; 33-70% of all carcinomas of the breast had isolated metastases (hypernephroma up to 65% and bronchial carcinoma up to 41%). Indication for extirpation depends on the localisation, position and size of the metastasis and the absence of further tumour centres in the body. Out of 45 radically operated patients, nine (20%) lived longer than one year after operation. In 1067 autopsied patients, carcinoma of the breast was the second most frequent primary tumour with multiple metastases in the brain (231 cases = 22%). In bronchial carcinoma, the rate was somewhat higher (364 = 34%).

Lung

Kulka and Baradnay[5] found two cases of carcinoma of the breast as primary tumour among 12 isolated metastases of the lungs. After lobectomy, the patients lived a further nine and 12 months respectively. Kelly and

*See editorial page 1119.
†From the Surgical Department of the University of Giessen (Director: Prof. K. Vossschulte).

Langston observed that out of 22 patients with solitary pulmonary metastases none had a primary carcinoma of the breast. Out of 254 patients with isolated metastases of the lungs, a carcinoma of the breast in 31 cases was the primary tumour. Only two of the resected patients lived longer than five years.[12]

Femur and Humerus

In solitary metastases in the region of the joints of the femur and humerus, resection of the pathological part of the bone can be attempted, followed by replacement with an endoprosthesis. This operation ensures the patient sufficient use of the extremity. It can also be performed on patients over 70 years of age as seen from the good results obtained with 100 hip endoprostheses (Moore) inserted because of normal or pathological medial fractures of the femoral neck.[2]

Amputation and exarticulation of the entire extremity should be avoided in metastases of carcinoma of the breast. One must always reckon with the appearance of further metastases, for example, in the spine or pelvis. The loss of the entire extremity is then, retrospectively, a severe psychological trauma which could have been avoided. Here, one must distinguish between the metastasis of the carcinoma of the breast and the primary sarcoma for which amputation or exarticulation of the extremity is often essential. The necessity for such a mutilating operation appears to be justifiable, therefore, only in special cases of metastases of mammary carcinoma, as it is doubtful whether the operation is radical in these patients.

Thus, even in cases with isolated metastases, the author attempts to prevent threatening fractures of the diaphysis of the long bones with the help of a marrow nail. Stable osteosyntheses are performed in patients with pathological fractures in order to avoid prolonged immobilisation and to restore the use of the limb as far as possible. The technical simplicity and excellent results of marrow nailing can easily be achieved in smaller hospitals and the operation can be performed on almost all patients. Unstable osteosyntheses which require additional external fixation of the extremity are of no advantage to the patient and should be avoided.[11]

The Giessen Series

Between 1960 and 1968, 464 female patients were treated in this hospital for carcinoma of the breast. Mastectomy with removal of the axillary lymph nodes was carried out in 405 cases. The patients were mainly in Steinthal stages I and II. A simple mastectomy was performed in 43 patients in stage III in order to remove an ulceration of the tumour or to prevent infiltration into the deeper layers of the chest wall. Even this palliative operation could not be carried out in 16 patients in stages III and IV. According to Hagensen and coworkers[3] and Schwaiger,[9] even in stages I and II, 20% and 50% of the patients respectively must be considered as having metastases in the parasternal and supraclavicular lymph nodes. Their complete removal is always uncertain and there is a marked risk in older patients. If the radical operation is performed early, the five-year survival rate is 70-80% for patients in stage I and 30-40% for patients in stage II.[7,8]

Patients in all stages were transferred for radiation therapy and radiological inactivation of the ovaries after healing of the wound. No intra- or postoperative cytostatic treatment was carried out.

In the last nine years, 23 patients have been hospitalised in the Surgical Department of the University of Giessen for metastases of a breast tumour. In 19, the carcinoma of the breast had occurred two to 14 years previously. Twelve of them had received radiation therapy. Three of the women underwent immediate simple mastectomy in the Department.

Isolated Metastases

Isolated metastases could be removed only

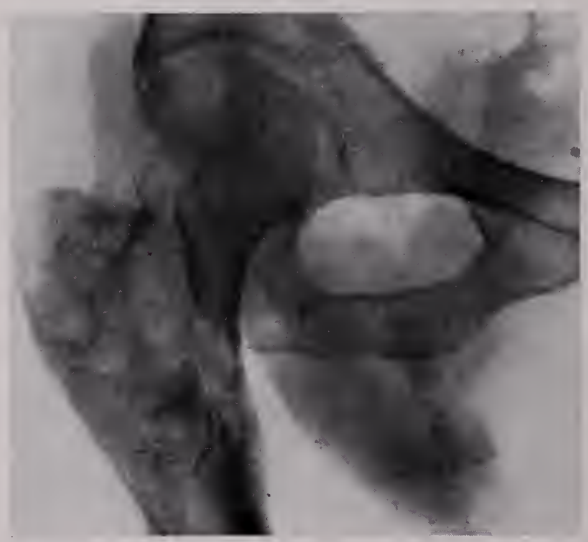


Fig. 1—Oblique view of right pelvis of a 41-year-old woman. Indistinct structure of the trochanteric area with spherical centres of osteolysis. Larger osteolytic centre in the ischial tuberosity.

by radical operation in three patients. In a 41-year-old patient, osteolytic metastases in the right ischial tuberosity and trochanter appeared three years after right-sided mastectomy for a scirrhous carcinoma (Figure 1). After excluding the possibility of further metastases, bilateral ovariectomy and resection of the ischial tuberosity and proximal third of the trochanter were performed in two operations. The femoral neck and shaft of the trochanter were replaced with an endoprosthesis (Figure 2a). Two years later, it was necessary to remove the prosthesis on account of static symptoms in the right hip joint and replace it with a more suitable prosthesis (Figure 2b). Eight years after the radical operation, the patient is free of metastases and can walk with the help of a cane. The last x-ray control showed progressive excavation of the acetabulum due to pressure osteolysis (Figure 3).

Scapula Metastases

A 65-year-old patient was referred because of a radiation-resistant metastasis in the right shoulder blade 14 years after mastectomy. As no other metastases were found, resection of

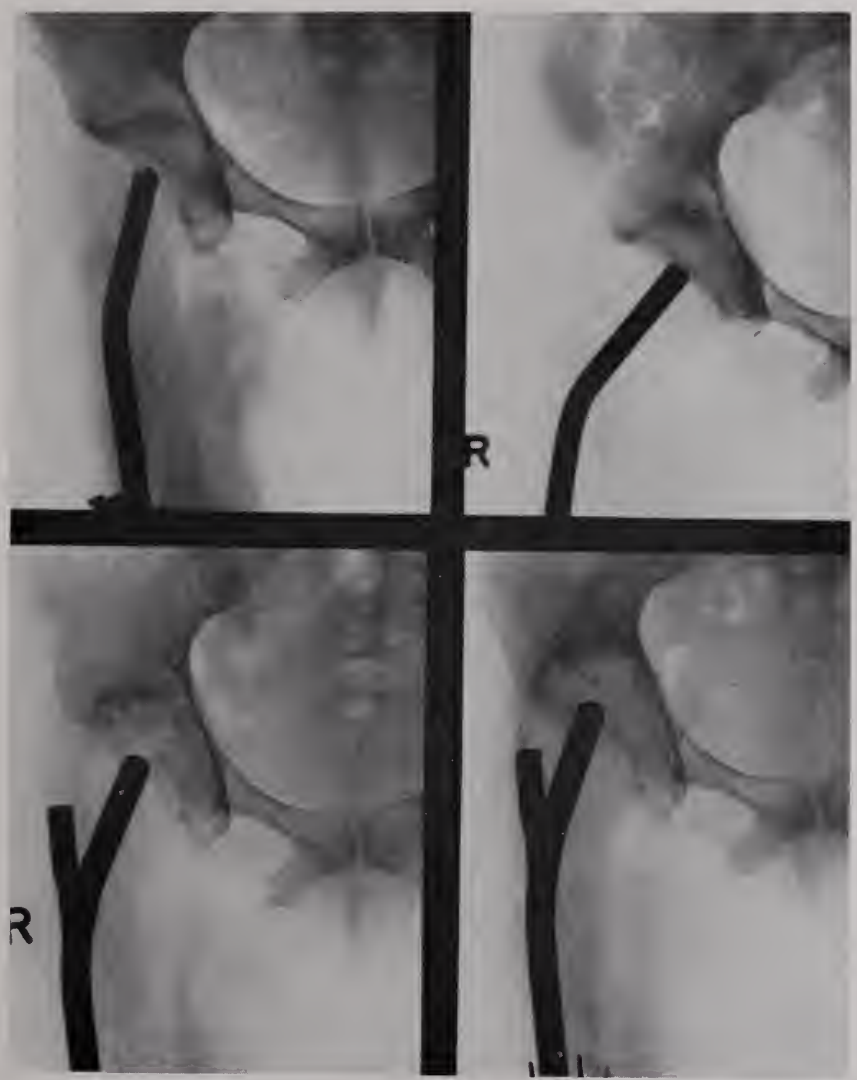


Fig. 2A (top)—Anteroposterior view of the right pelvis seven months postoperatively. Situation after the replacement of the proximal third of the femoral shaft by a metal prosthesis and partial resection of the ischium. Widening of the acetabulum. Slight decalcification. Fig. 2B—(bottom) Anteroposterior view of the right pelvis two years after exchange of the endoprosthesis. Further widening of the acetabulum with sclerosis of the rim and patchy decalcification in the region of the acetabulum.

the shoulder blade was recommended, so that the patient still had restricted use of the hand. This is a small operation as compared to interthoracoscapular amputation, but the decision proved to be correct when metastases appeared in the right clavicle and left ischium a few months later. The latter were treated with radiation (Betatron 9 Me V).



Fig. 3—Anteroposterior right hip joint five years after exchange of the endoprosthesis. Further widening of the acetabulum and sclerosis as a result of pressure osteolysis. Calcification of the soft tissue. No tumorous destruction of bone.

Interthoracoscapular Amputation (2 cases)

A 51-year-old patient was referred from the neurologist for a palliative operation six years after mastectomy and radiation therapy because of lymphatic oedema and continuous, unbearable pain in the left arm due to the invasion of lymph node metastases in the brachial plexus, which could not be alleviated. Apart from a radiogenic ulcer of the left chest wall, the patient is free of metastases three years after operation and has no subjective symptoms. The radical operation was carried out because of the severe pain and it was in no way certain that it would be a success.

Although metastases of the lungs and ribs were found in a 54-year-old patient, an interthoracoscapular amputation had to be performed because of a generalised septic infection caused by disintegrating metastases in the left shoulder joint. The radical operation eliminated the sepsis and there was subjective improvement, but the patient died eight months later from the pulmonary metastases.

Stabilizing Osteosynthesis

Of the remaining 19 patients, eight were hospitalised because of threatened or existing pathological fractures of the upper arm or thigh, three of them immediately after radiological discovery of the metastases. The spontaneous fractures could be prevented by marrow nailing, and the existing fractures were repaired by stable osteosynthesis. In one of the eight patients, a metastasis had already been removed from the occipital brain. Eleven of the patients were treated by radiation therapy because of multiple metastases in the lungs, pleura, lymph nodes and bones. The extensive spread of the carcinoma excluded even a palliative operation in these patients.

In spite of great progress in diagnosis and operative technique, complete healing is very rarely achieved when metastases of breast carcinoma have appeared. It is a characteristic of the primary tumor that metastases are formed late but then become generalised, particularly in the vertebrae, ribs and lungs. However, the unsatisfactory results reported are no cause for resignation. Apart from very rare

cases in which radical removal of a solitary metastasis is achieved, palliative operations often contribute much to the well-being of the patient by reducing pain and making the remaining months of life to some extent bearable.

Summary

The possibility of operative removal of metastases of carcinoma of the breast is limited. Solitary metastases can be extirpated in the brain and healed by resection or amputation in the bones. A stable osteosynthesis is preferable in cases of threatened or existing pathological fractures due to bone metastases.

Out of a total of 23 patients, metastases could be removed radically only from the pelvis, tibia, shoulder blade and axilla in three of them. Eight patients underwent osteosynthesis as a palliative operation for pathological fractures. No operation could be performed in 11 patients because of generalised metastases.

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The Pig

Pig of My Heart—So much of our indebtedness to you is taken for granted that I want to write you a few lines of appreciation. For your friendliness to man knows no abatement; I believe that every day you come to our rescue more and more; every day, all over England, to the traveler's question, "What have you for lunch?" the answer is more frequently returned, "I'm sorry, but there's nothing but eggs and bacon." The innkeeper's sorrow matters nothing, because directly we hear the word bacon our hearts leap up.

A lot of rubbish has been talked (and sung) about the roast beef of Old England. The national dish of this great country is bacon—a gift from you. Eggs no doubt can be an agreeable accessory, but it would be an ungracious act in a letter intended to celebrate your merit to stress them overmuch. Bacon alone is food for the gods.

But bacon is not all. What of ham? What of brawn? What of pork? What of Bath chop? What of sausages? All these blessings we owe to you. Forgive me, however, if I am dwelling too long on what, after all, cannot be unmixedly agreeable hearing for yourself, since, in order to give us these noble dishes you must first have passed away.

Finally, a word of thanks for your assistance in helping us out in invective—I am sure not by your own wish, but very usefully none the less. The people that we don't like, whether for particular or general reasons—what do we call them? We ought really to search our minds for the accurate epithet minutely applicable to each; but we are too lazy for that. So—very unfairly—we fall back on you and merely say they are pigs. The child who eats too quickly, the man who won't have the window open in the railway carriage, the woman who edges her way unjustly into a queue, the boy who demurs at the punctual bath—each is rapidly characterized as a pig. As I say, it saves us trouble to think no further and to borrow your name in this way; but it isn't fair, because they did not go to you to learn these habits; they were behaving naturally.*

*Edward Verrall Lucas (1868-1938).

Cephalus to Socrates on Old Age

Socrates: To tell you the truth, Cephalus, I delight in conversing with very old persons. For as they have gone before us on the road over which perhaps we also shall have to travel, I think we ought to try to learn from them what the nature of that road is—whether it be rough and difficult, or smooth and easy. And now that you have arrived at that period of life, which poets call 'the threshold of Age,' there is no one whose opinion I would more gladly ask. Is life painful at that age, or what report do you make of it?

Cephalus: I will certainly tell you, Socrates, what my own experience of it is. I and a few other people of my own age are in the habit of frequently meeting together, true to the old proverb. On these occasions, most of us give way to lamentations, and regret the pleasures of youth, and call up the memory of amours and drinking parties and banquets and similar proceedings. . . . Some also complain of the manner in which their relations insult their infirmities, and make this a ground for reproaching old age with the many miseries it occasions them. But in my opinion, Socrates, these persons miss the true cause of their unhappiness. For if old age were the cause, the same discomforts would have been also felt by me, as an old man, and by every other person that has reached that period of life. But, as it is, I have before now met with several old men who expressed themselves quite in a different manner; and in particular I may mention Sophocles the poet, who was once asked in my presence, 'How do you feel about love, Sophocles? are you still capable of it?' to which he replied, 'Hush! if you please: to my great delight I have escaped from it, and feel as if I had escaped from a frantic and savage master.'

I thought then, as I do now, that he spoke wisely. For unquestionably old age brings us profound repose and freedom from this and other passions. When the appetites have abated, and their force is diminished, the description of Sophocles is perfectly realized. It is like being delivered from a multitude of furious masters. But the complaints on this score, as well as the troubles with relatives, may all be referred to one cause, and that is, not the age, Socrates, but the character of the men. If they possess well-regulated minds and easy tempers, old age itself is no intolerable burden: if they are differently constituted, why in that case, Socrates, they find even youth as irksome to them as old age.

Be assured, Socrates, that when a man is nearly persuaded that he is going to die, he feels alarmed and concerned about things which never affected him before. Till then he has laughed at those stories about the departed, which tell us that he who has done wrong here must suffer for it in the other world; but now his mind is tormented with a fear that these stories may possibly be true. And either owing to the infirmity of old age, or because he is now nearer to the confines of the future state, he has a clearer insight into those mysteries. However that may be, he becomes full of misgiving and apprehension, and sets himself to the task of calculating and reflecting whether he has done any wrong to anyone. . . . But if his conscience reproaches him with no injustice, he enjoys the abiding presence of sweet Hope, that 'kind nurse of old age,' as Pindar calls it.*

*The Republic of Plato, Book I.

Percutaneous Catheter-Arteriographies*

Seldinger Technique

N. HEGER, M.D.,† S. BAYINDIR, M.D.,† R. STECKENMESSER, M.D.† and H. SCHIRMER, M.D.†

THE INTRODUCTION of the Seldinger technique together with a well tolerated, water-soluble contrast medium is a significant advance in angiography which has led to a marked increase in radiological examinations of the blood vessels. Just as in direct arteriography, a certain risk is involved in catheter angiography. Reports on the results of angiography have been followed by those dealing with the complications.

On the basis of the material collected by the authors and the results reported in the literature, the present risks in catheter arteriography using the Seldinger technique are evaluated. The term complication is reserved for the severe incidents summarised in Table 3.

Material and Methods

Catheter angiographies using the Seldinger technique have been performed 1682 times during the last five and one-half years in the Department of Surgery of the University of Giessen (1/1/64 to 1/7/69).

Area Examined

Table 1 shows the angiographies grouped according to the vascular area examined. The trans-femoral approach was used almost exclusively. Children and young adults were examined with the red Oedman-Ledin catheter (*PE 160*). The same catheter was used for the axillary and brachial angiographies. The yellow Oedman-Ledin catheter (*PE 205*) was used for the other examinations.

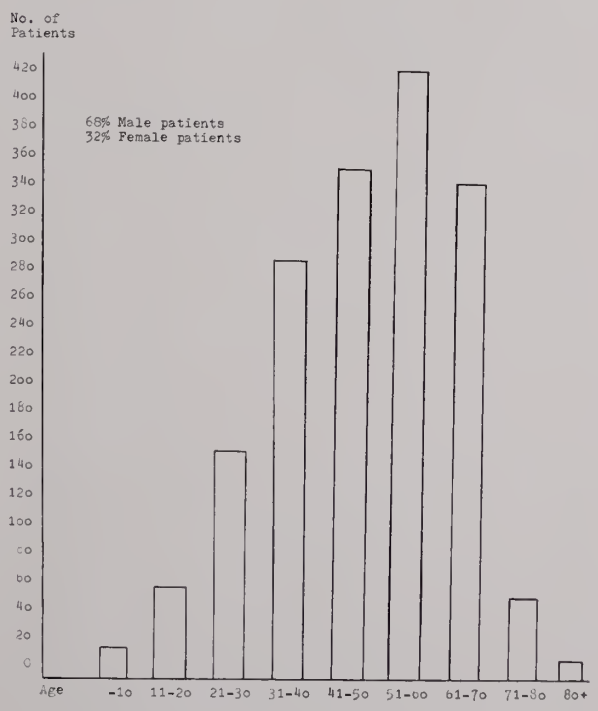
Age Distribution

The Figure shows the age and the sex of the patients. The youngest patient was four years old and the oldest 82; the age peak lay between 51 and 60 years. Of the angiographies 84% were performed under local anaesthesia, 13% in intravenous narcosis, and 3% with intubation anaesthesia. Examination of blood coagulation was made as a routine laboratory procedure before each angiography. Angiography was performed only rarely when the Quick value was below 50. Twenty-four hours of bed-rest is recommended after the procedure. The effect of

TABLE I

Classification of the 1682 Transfemoral and Transaxillary Catheter Angiographies with the Seldinger Technique

Aortography (thoracic, abdominal)	315
Demonstration of the pelvic vessels (Tumours of the bladder)	64
Demonstration of the femoral artery and pelvic vessels	543
Demonstration of the femoral artery	98
Axillary + brachial arteriography	67
Selective coeliacography and mesentericography	217
Selective coeliacography	104
Selective renovasography	263
Selective demonstration of the lumbar vessels	10
Selective demonstration of the intercostal vessels	1



Figure—Age and sex of patients examined.

*See editorial, page 1121.

†From the Radiological Section (Head: Dr. med. S. Bayindir) of the Surgical Department of the University of Giessen (Director: Prof. K. Vossschulte).

the compression dressing was enhanced with a sand bag.

Method

An AOT-sheet film changer (Elemma-Schönander, film size 35 × 35 cm) was used for the serial angiograms; a special modification of the Gärtner-Reiser changer was used for the majority of the femoral angiographs (film size 20 × 90 cm).

A Jothalamate (Conray®, Fa. Byk-Gulden, Constance, Germany) has been employed exclusively as contrast medium since the beginning of 1966 and has been applied in a total of 1374 patients.

Arteriography of the femoral artery is included among the catheter angiographies, as a short Oedman-Ledin catheter approximately 10 cm long was used in place of the Seldinger injection cannula. The advantages of the short catheter are: 1. its easy, safe insertion into the vessel, 2. its remaining in place when the position of the patient is changed (Bayindir et al. 1966).

Observations

Severe complications were observed 14 times = 0.8% (Table 2). There were no deaths.

TABLE 2

Type and Number of Complications

Complication	Number	Operative Treatment	Conservative Treatment
Bleeding or extensive haematoma at site of puncture	5	1	4
Extensive haematoma of the abdominal wall (Penetration of the guide into the inferior epigastric artery with rupture of the vessel)	1	—	1
False aneurysm (aneurysma spurium)	2	2	—
Arterial thrombosis at the level of the puncture site	3	3	—
Arterial embolism	1	—	1
Complication due to contrast medium	1	—	1
Central nervous dysfunction	1	—	1

Hemorrhage

Extensive haematoma at the site of puncture which necessitated conservative treatment and prolonged the hospitalisation up to 14 days occurred in four cases. One haematoma the size of a double fist had to be treated surgically. Three of the patients were severely obese and two had marked hypertension. In one patient, a massive haemorrhage in the region of the left lower quadrant of the abdomen occurred when we tried to introduce the guide from the left femoral artery into the aorta. The guide entered the atypical left inferior epigastric artery, damaging the vessel and causing a haematoma. The latter regressed completely with conservative treatment.

False Aneurysm

Two surgical interventions were necessary because of the development of false aneurysms (aneurysma spuria) in the inguinal region. The first patient was a 59-year-old obese woman who underwent angiography because of suspected renal hypertension (BP 250/130). Several punctures had been attempted. After examination, a large haematoma formed at the site of puncture and the usual pressure dressing was applied. An after-bleeding occurred on the way to the ward. Two days later a stenotic murmur was heard over the haematoma. At operation, a partially thrombosed aneurysm was removed, the stalk of which corresponded to the ruptured inferior epigastric artery. The postoperative course was uneventful.

The second case occurred in a 57-year-old patient who had had an upper arteriography through the femoral artery because of a suspected stenosis of the carotid artery. A massive haematoma was found at the site of puncture which was first treated conservatively. However, it showed no tendency to regress and extensive bleeding occurred on the tenth day after angiography, which necessitated immediate operation for the repair of a false aneurysm which was found to be due to a tear 2.5 cm long in the femoral artery at the level of bifurcation of the deep femoral artery. After an uneventful postoperative course, the carotid stenosis which had been diagnosed angiographically was removed by operation.

Arterial Thrombosis

On three occasions, arterial thromboses were caused at the site of puncture (two in the femoral artery and one in the brachial artery). In all three cases, thrombectomy restored the original flow rate. In two cases the arterial blockage occurred immediately after the examination, and in one case two days later. Two of the patients had a disease of the pancreas, one with a marked tendency to thrombosis.

The third patient had had a severe trauma of the upper arm six months before angiography with marked defects of the soft tissues and lesions of the nerves and vessels. Angiography revealed a filiform narrowing of the brachial artery about 10 cm long in the region of the injury; thrombosis occurred at the site of puncture. On operation, the artery was found to be blocked by hard scar tissue and thrombosed for a length of 0.5 cm.

Embolism

A peripheral embolism was found in the lower leg of a 40-year-old woman when the short yellow Oedman-Ledin catheter was positioned for arteriography of the femoral artery. Injection of contrast medium revealed a blockage of the popliteal artery. The foot pulses could be palpated again after two days' treatment with thrombolytic medication.

Shock-Like Reaction

On one occasion angiography of the coeliac artery had to be discontinued because the patient vomited violently and collapsed ten seconds after the trial injection of approximately 5 ccm of contrast medium. The condition was rapidly relieved after the administration of circulatory stimulants and oxygen.

Hemiparesis

A right-sided hemiparesis and blindness occurred immediately after the injection under pressure (6 atm) of the contrast medium in a 63-year-old patient who was catheterised from the right axillary artery for an aneurysm of the abdominal aorta. The catheter lay in the aortic arch before the injection of the contrast medium. Marked cyanosis was also observed which rapidly disappeared under the immediate administration of oxygen. The dysfunction of the central nervous system could no longer be detected after two days. The incident was caused by considerable amounts of contrast medium streaming into the vessels of the brain under high pressure.

Discussion

Demonstration of the arterial system with contrast medium radiography has become a hospital routine. In spite of the improvement in angiographic techniques,[26] and the use of well-tolerated contrast medium (jothalamate, diatrizoate), there is a certain risk because of:

1. Mechanical manipulation (puncture of the vessels, introduction of the guide and catheter, probing of the desired artery).
2. Increase in intravascular pressure during injection.
3. Application of the contrast medium.

A few large statistical series (over 1000 cases) dealing with the complications in angiography using the Seldinger technique have been published (Table 3). Most of the incidents reported, however, relate to a smaller number of evaluations or are reports of isolated cases. In the two largest series published up to the present (11,402 and 6,155 cases), the mortality due to catheter angiography is given as 0.06% and 0.05%.[16,23,24] Severe complications in 0.4% to 3% of the cases have been re-

TABLE 3

Statistics from the Literature + the Authors' Examinations of the Deaths and Severe Complications* after Transfemoral + Transaxillary Catheter Angiography Using Seldinger's Technique.

Year	Author	No. of Examinations	Deaths	Severe Complications
1963	Lang, E. K. Sammelstatistik	11,402	7=0,06%	81=0,7%
1963	McGraw, J. Y.	372	—	5=1,4%
1964	Sauer, H. Th. Sammelstatistik	6,155	3=0,05%	110=1,8%
1964	Halpern, M.	1,000	—	22=2,2%
1964	Kottke, B. A. et al.	195	—	6=3,0%
1966	Seidenberg, B. a. E. S. Hurwitt	1,500	—	26=1.7%
1966	Bessler, W. u. H. Spies	500	—	2=0,4%
1966	Raschke, E. u. H. J. Maurer	244	—	7=2,8%
1968	Folin, J.	1,319	—	16=1,2%
1968	Diemel, H. u. H.-G. Schmitz-Drager	241	—	7=2,9%
1969	Heger, N. et. al.	1,682	—	14=0,8%

*Severe complications: Marked after-bleeding from the puncture wound, massive haematoma at the site of puncture, perforation of the vessel, dissection of the arterial wall, false aneurysms, thrombosis (arterial-venous), peripheral embolism, breaking off of the point of the guide, renal damage, cerebral damage, complications due to the contrast medium.

ported. In this series, 14 (0.8%) severe incidents occurred in 1682 angiographies.

After-bleeding—Haematoma—Aneurysm

Slight bleeding from the puncture wound occurs in almost every angiographic catheterisation in spite of sufficient compression. The small haematomas that result are rapidly resorbed, but can become infected. Obese patients with hypertension are particularly liable to after-bleeding. Manual compression must be sustained for a sufficient length of time in these patients, but the pressure should not be too great because of the danger of thrombosis.[20] Perforation of the posterior wall of the artery or vascular tearing by the puncture cannula, guide or catheter can result in severe uncontrollable bleeding and false aneurysms. False aneurysms have been relatively rarely reported. They have to be surgically treated because they can increase in size and perforate.

The guide and the following catheter can easily penetrate the subintimal layers of the vascular wall if there are advanced degenerative changes of the arteries.[10,27] Injection under pressure then causes a dissecting aneurysm. A dissection in the region of the aorta with compression of the renal or mesenteric vascular stem is a dangerous situation.[19] Such incidents can be avoided by a trial injection of a few ml of contrast medium with radiological control. The position of the catheter can thus be checked. Before the pressure syringe is connected, blood must emerge in spurts from the end of the catheter.

Arterial-venous shunts at the level of the puncture are very rare complications which can arise when the femoral vein and artery are punctured simultaneously. They must be treated operatively because of the resulting cardiac strain.

Thrombosis—Embolism

According to the literature, arterial thromboses at the site of puncture are responsible for almost half of the severe complications.[3,11,25] Several factors are responsible:

1. Trauma of a previously damaged arterial wall (arteriosclerosis) by repeated attempts at puncture.
2. Lesions of the intima due to the forced insertion of the guide or catheter.
3. Use of poorly prepared or worn down catheters (fraying of the point).
4. Prolonged periods of catheterisation.
5. Exaggerated and prolonged compression at the end of the examination.
6. Vascular spasms.
7. Disturbances of blood clotting (hypercoagulability).

Apart from arterial obstruction, thromboses of the femoral vein have also been described.[8]

Arterial embolism after angiography can be divided according to the time of appearance into early and late embolism. An embolism can be caused by detached arteriosclerotic plaques and atheromatous material, thromboses at the point of the catheter and clumps of thrombocytes from the damaged intima. Embolitic dispersion of foreign material can also occur when the point of the flexible guide breaks off. This complication was found in eight out of a total of 6155 angiographies.[23,24] In most cases, the broken point must be left in situ.

Complications Due to the Contrast Medium

Anaphylactic reactions and severe deleterious allergies due to contrast medium are a recognised danger but are very infrequent. According to the results of the large statistical series, there are nine to 12 deaths per million injections of contrast medium.[21] An increase in plasmakinin after the injection of contrast medium has been found in animal experiments.[9] Lack of reaction after the preliminary injection of the contrast medium does not imply that there will be no severe complications. Knowledge of the best treatment for these complications is far more important than the preliminary testing.

Renal Damage

Oliguria and anuria have been described after repeated applications of large quantities of contrast medium in the renal arteries.[14] Forty-six deaths due to renal failure after aortography were described in the American literature up to 1957.[6,19] On the basis of animal experiments, post-angiographic damage to the kidneys has been found to be due to the ischaemia caused by the injection.[18]

Cerebral Damage

There are numerous reports of animal experiments relating to damage to the brain by the contrast medium.[5] The amount, concentration and length of application of the contrast medium are decisive for the formation of disturbances in permeability of the blood brain barrier. There are only a few seconds between the commencement of the injection and the appearance of pathological changes; the effects can be cumulative on repeated injections. In the case reported in this paper in which central dysfunction appeared shortly after the application of the contrast medium, complete regression of the symptoms was observed after two days. Acute paraplegia following angiographic examination should also be included here. It is very rarely observed and is thought to be due to an ischaemia of the lumbar and lower thoracic spinal cord due to prolonged hindrance of the circulation in the major radicular artery.[13]

Catheter angiographies are indispensable to modern diagnosis and are performed in specially equipped hospitals in large numbers. A mortality rate of 0.05%-0.06% and about 1% of severe complications can be regarded as an acceptable risk.

Summary

The complications in 1682 catheter angiographies using the Seldinger technique (14 = 0.08%) are comparable with those reported in the literature. The risk is regarded as acceptable.

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School of Salernum

Of washing of your hands much good doth rise,
'Tis wholesome, cleanely, and relieves your eyes.

—Regimen Sanitatis Salerni

Editor's Note: Though I hadn't thought of it before, the School had a rather subtle, sardonic method of relieving conjunctivitis in the days when murine might have been sea water.

The first forty years of life give us the text; the next thirty supply the commentary.—Arthur Schopenhauer

Hypothalamus and Politics

Political Tantrums

Prince Otto von Bismarck, popularly known as the Iron Chancellor, once confided to the English painter Richmond that he was "all nerves." At the Battle of Koniggratz he was overcome by nervous fits of weeping. When severely annoyed he would vomit gall and take to his bed in a rage, both reactions mediated through the hypothalamus. Outwardly a symbol of concentrated power, to his wife Bismarck was just a "poor sick duck."

Emotional behavior verging on the maniacal was also the gaudier side of Napoleon's character. Under the influence of hypothalamic reactions, he could throw a prince out of the room, kick a venerable senator in the stomach, smash costly chinaware to break down an Austrian envoy's resistance, and rant and rave at Metternich for nine hours at a stretch. He once admitted that "my nerves are irritable," a superbly imperial understatement.

Closer to our own time, the most loathsome representative of hypothalamic politics was Adolph Hitler. He lived in a self-created atmosphere of what some have called "temperamental heat" or "raving excitement." His explosions of fury bordered on mania, though whether he actually chewed carpets is a debatable biographic point. When he was appointed Chancellor, he burst into tears; when he heard of the French capitulation in 1940 he danced a jig of joy. Alternately frenzied and morbidly despondent, the late dictator was a prime example of behavior under the rule of the thalamus.*

*Felix Marti*Ibanez: The Pageant of Medicine, 1960.

Editor's Note: Any of your acquaintances come under this characterization?

Return To Aesculapius

By 500 B.C. Alcmaeon had insisted on the doctrine "health depends upon harmony, disease upon discord of the elements within the body." This, however inadequately achieved, was the aim of the Aesculapian cult. In our own day the development of scientific medicine did for a time divert attention from the patient as an individual. The rise of morbid anatomy, bacteriology, and bio-chemistry in turn tended to this. But medicine is a department of biology and unless we consider the patient as a whole, as a living organism reacting to changes in either the external or the internal environment, we shall miss an essential part of his case. Ordinary materialistic medicine is apt to forget the fact that the patient's emotional and mental outlook will inevitably influence, and be influenced by his disease; the psychotherapist is apt to forget that the patient has a body which may be suffering from some physical distress.*

*Sir Walter Langdon-Brown: Thus We Are Men, 1969.

Editor's Note: I'm sure that old Doc Aesculapius would have combined them all had he known the scientific facts as we know them.

Massive Gastrointestinal Haemorrhage

G. SPITZER, M.D.* and K. ZIMMERMANN, M.D.*

Gastrointestinal haemorrhage is an alarming event for both the patient and the physician. The agitation is not unfounded, because the mortality quoted by various authors lies between 3-30%. In this study, an average mortality of 19.9% was found. It varied according to the disease underlying the bleeding.

Definition

Even the definition of massive acute gastrointestinal bleeding is difficult. The absolute blood loss related to the normal amount of circulating blood would be an objective measure (Dick), but this is difficult to determine; it can be measured exactly only with I^{131} labelled human albumin in the volumetron. However, this apparatus is not available in all hospitals.

Intensity

The intensity of bleeding, i.e., the blood loss/unit time, can be roughly estimated only with the help of laboratory tests, clinical control of the patient and the observations of the physician.

Laboratory tests include routine haemoglobin, erythrocyte count and haematocrit. It is known that these values do not give exact information on the intensity of bleeding as they usually lag behind the actual condition of the patient. Clinical evaluation of the patient includes observation of blood pressure, the need for replacement, pulse and venous pressure and course of the bleeding, such as the volume of urinary excretion.

Source of Bleeding

Source

The source of bleeding is indicated from its character, probability, anamnesis† and, above all, x-ray examination.

The nature of the bleeding[12] which is a combination of direction (vomiting, faeces), colour (clear red, black), and intensity can give a good indication of the source.

The probability of the most likely source of bleeding is no diagnosis but can be of help in looking for the source. Reifferscheid[12] states that 85% of acute massive gastrointestinal bleedings arise in the stomach and oesophagus. This number was more or less confirmed in this study; 72.5% of the haemorrhages originated in the stomach or oesophagus.

History

The anamnesis is important in tracing the source of bleeding. Anamnesis of an old ulcer or liver disease guides the examination in a particular direction.

However, radiological examination, even during acute bleeding, is the most successful method of obtaining a diagnosis. Many authors agree with this opinion.[2,9,12,14]

Method of Therapy

In the question of therapy, there is no fixed scheme of treatment. At the time of Gustav

TABLE I

Operative Methods Used in Oesophageal Varices Between 1959 and 1968

1959	Dissection ligature	3
1960	Dissection ligature	7
1961	Dissection ligature	2
	Purse-string ligature	1
	B II on account of stomach varices	1
1962	Dissection ligature	2
1963	Dissection ligature	6
	Portacaval anastomosis	5
	Talma operation	1
1964	Portacaval anastomosis	1
1965	——	
1966	Portacaval anastomasis	1
1967	Portavacal anastomosis	5
	Extirpation of the spleen	1
1968	Portacaval anastomosis	3
Total		39

*From the Surgical Department of the University of Giessen (Director: Prof. K. Vossschulte).

†See Test Your Word Score, page 1131.

von Bergmann and Victor Schmieden, there was bitter discussion as to whether massive gastrointestinal bleeding should be treated by the internist or the surgeon. Today, fortunately, there is general agreement that the problem belongs neither to the surgeon nor to the internist, but is a joint task. The opinion as to the time of operation is not unanimous. Finsterer[4] waited 48 hours and then, as the first surgeon to do so, recommended operation to still the bleeding. Zuckschwerdt[17] operates when there is no improvement after eight hours and the transfusion of 500 ccm blood. Wachsmuth[14] classified the operations according to time. In the emergency operation, there are only hours between the onset of bleeding

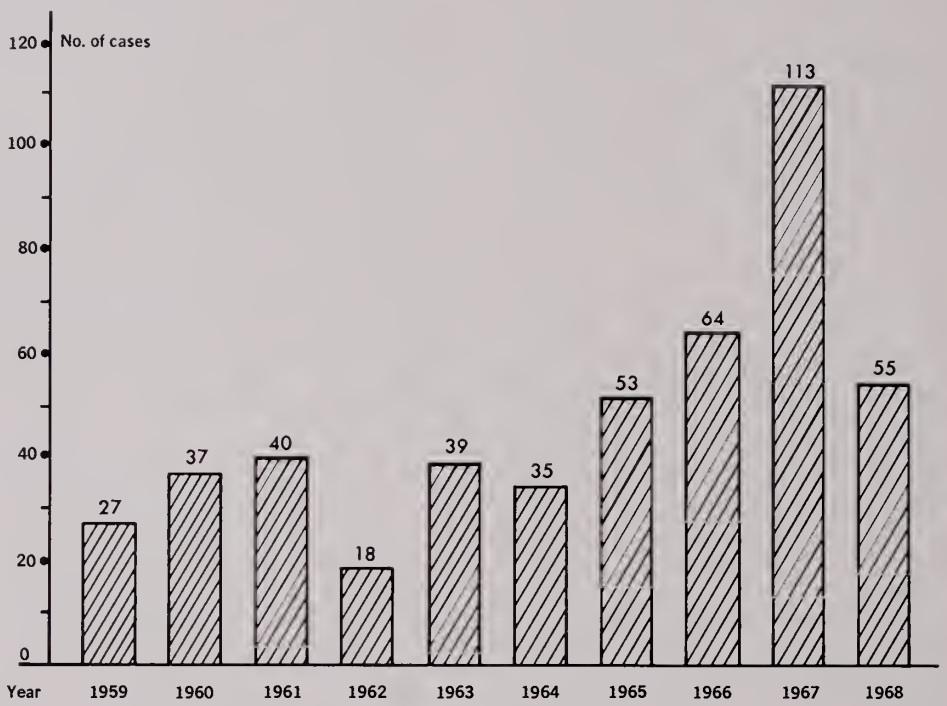


Fig. 1—Increase in number of massive gastrointestinal bleedings between 1959 and 1968.

PART I OF TABLE 2.

Summary of the Number and Results of Treatment of Massive Gastrointestinal Haemorrhage Between 1958 and 1969

Year	No.	♂	♀	Duod. Ulcer	Treatment		Ventr. Ulcer	Treatment	
					Oper.	Cons.		Oper.	Cons.
1959	27	18	9	3	2	1(+ 1)	1	1(+ 1)	
1960	37	26	11	13	10(+ 2)	3(+ 1)	3	1	2
1961	40	29	11	16	9(+ 2)	7(+ 2)	5	4(+ 1)	1
1962	18	14	4	2	2		2	2	
1963	39	25	14	3	2(+ 2)	1	5	3(+ 1)	2
1964	35	24	11	13	4	9(+ 2)	6	6(+ 3)	
1965	53	37	16	19	8(+ 2)	11(+ 2)	17	14(+ 3)	3
1966	64	45	19	12	9	3(+ 3)	15	11(+ 1)	4(+ 3)
1967	113	74	39	28	12(+ 3)	16(+ 4)	22	10(+ 1)	12(+ 3)
1968	55	38	17	13	6(+ 2)	7(+ 1)	8	7	1
Total	481	330 68.6%	151 31.4%	122 25.3%	64(+13) 52.5%	58(+16) 47.5%	84 17.5%	59(+11) 70.2%	25(+ 6) 29.8%

and operation; in these cases, the bleeding is so severe that one must operate to save the life of the patient (mortality 29%). In the elective operation, the intensity of the bleeding allows sufficient time to bring the patient into the best possible general condition under the circumstances, which can be more than 48 hours (mortality 3.2%). In the interval operation, time of operation is determined after the bleeding has been stopped conservatively (mortality 0%).

In addition, the basic question as to whether or not one should operate after the bleeding has been stopped conservatively is still under discussion.

Giessen Series

Four hundred and eighty-one patients with acute gastrointestinal haemorrhage were treated in the Surgical Department of the University of Giessen between 1959 and 1968. There were 330 (68.6%) male and 151 (31.4%) female patients. All who were found from the Documentation Department to have had acute gastrointestinal bleeding were statistically analysed.

A clear increase in gastrointestinal bleeding was found during the 10-year examination period; during the years 1959-1964, there was an average of 32 patients a year. This number rose to 71 a year in the years 1965-1968. The reason for this increase may be due to prolonged life expectancy (Figure 1).

Underlying Cause

When classified according to the main diseases underlying the bleeding, the results were obtained as indicated in the illustration (Figure 2). Other authors arrived at the results shown in Table 3.

The differences found in the incidence statistics can be explained by the fact that various hospitals tend to specialise in different fields The data given for stomach and duodenal ul-

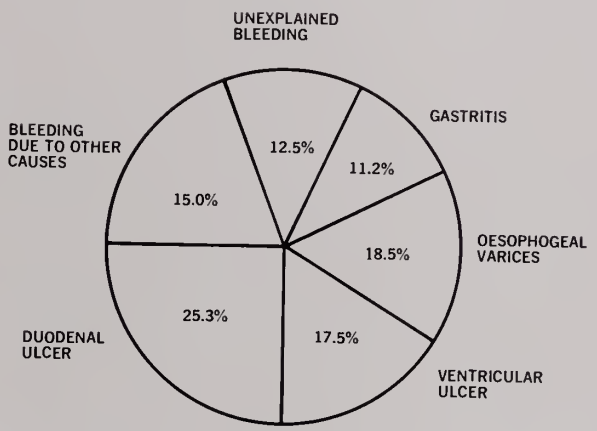


Fig. 2—Diagnoses of massive gastrointestinal bleedings.

PART 2 OF TABLE 2.

Summary of the Number and Results of Treatment of Massive Gastrointestinal Haemorrhage Between 1958 and 1969

Oesophageal Varices	Treatment		Gastritis	Treatment		Unexpl. Cases	Treatment		Others
	Oper.	Cons.		Oper.	Cons.		Oper.	Cons.	
4	3(+ 1)	1(+ 1)	5	1	4	8		8(+ 1)	6
11	7(+ 2)	4(+ 2)	2	2		5		5	3
9	4(+ 1)	5(+ 1)	6	3(+ 1)	3	4		4	
6	2(+ 1)	4(+ 1)	3	3(+ 1)		3		3	2
20	12(+ 5)	8(+ 4)	5	3	2	4		4(+ 1)	2
7	1	6(+ 3)	4	1	3	3		3(+ 1)	2
3		3(+ 1)	3	1	2	4		4	7
6	1	5(+ 4)	4	2(+ 1)	2	11		11(+ 3)	16
17	6(+ 4)	11(+ 5)	10	3	7	10	1	9(+ 1)	26
6	3	3(+ 2)	12	1	11(+ 1)	8	1	7(+ 1)	8
89	39(+14)	50(+24)	54	20(+ 3)	34(+1)	60	2	58(+ 8)	72
18	43.8%	56.2%	11.2%	37%	63%	12.5%	3.3%	96.7%	15%

cers vary between 42.8% and 80% so that our figures are the lowest. Those for oesophageal varices vary from 3% to 18.5% so that the highest percentage is reported in this study, in which only acute bleedings were included. The patients who did not have any bleeding but who underwent operation for portal hypertension are not taken into account. This high percentage may be due to the fact that the Surgical Department of the University of Giessen has studied the operative technique for portal hypertension for many years.

The marked differences in the percentages given for cases in which the source of bleeding was not found are very noticeable. Some authors do not quote any figures; in others the percentage varies from 2%-12.5%.

Surgical Procedure

There is no question of the necessity for operation in cases of bleeding from duodenal or ventricular ulcers either when there is a recurrence of bleeding from a chronic ulcer, or when the patient threatens to bleed to death in spite of conservative treatment. Stomach resection by Billroth II is the method of choice. The bleeding is most certainly stopped by this method and the patient healed from the basic complaint at the same time. A second laparotomy and suture of another bleeding vessel was necessary in only two patients. In occasional cases, when resection was impossible on technical grounds or if the patient was in poor general condition, the point of the bleeding was sutured. A second laparatomy was necessary in three cases because of continued bleeding. One hundred and seven stomach resections by Billroth II are compared with 12 purse-string ligatures performed between 1959 and 1968. In five cases other operative techniques were used.

Mortality

In the examination period 1959-1968, 122 (25.3%) bleeding duodenal ulcers were treated. Sixty-four (52.5%) were operated with a mortality of 20.3%. A mortality between 0%[8] and 28%[11] is reported in the literature. Fifty-eight (47.5%) were treated conservatively with a mortality of 27.5%. In other studies, the data vary between 6.5%[10] and 30.3%.[8] The mortality in bleeding ulcers is definitely correlative to the age of the patient. There was no mortality in patients with bleeding duodenal ulcers under 40 years of age. This is in agreement with the results quoted by Henning.[7] The mortality in patients over 40 was 23.7%. Death in operated patients with bleeding duodenal ulcers was due to haemorrhage in five cases; to heart and circulatory failure in four cases; to coronary infarction in one case, and in one case each, to pneumonia, uraemia and pulmonary embolism. In the group of patients treated conservatively, there were eight cases of fatal haemorrhage, five of cardiac and circulatory failure, two of pneumonia and one case of pulmonary embolism. Conservative therapy was used when the first bleeding could be arrested, if the patient was very old or in an

TABLE 3

	W. Heim 100 cases	Tanner 1658 cases	S. Mage 150 cases	W. Wachsmuth 288 cases
Ventricular		43%	16%	
Duodenal		32%	40%	
Ventricular and duodenal	64%			80%
Carcinoma of the stomach	15%	3%		13%
Oesophageal varices	6%	3%	16%	4%
Carcinoma of the oesophagus	2%			
Benign tumors	3%			
Gastritis	4%	6.8%	8%	2%
Peptic jejunal ulcers		4.3%	4.6%	
Hiatal hernia	1%			
Unexplained	2%		10%	
Polypus, hiatal hernia, aneurysm				1%

extremely poor general condition, or if operation was refused.

Ventricular Ulcer in Age

Eighty-four patients (17.5%) had to be treated in the hospital for their bleeding ventricular ulcer, 59 (70.2%) of whom were operated; the mortality was 18.6%. Twenty-five patients (29.8%) were treated conservatively; the mortality was 24%. In these cases, the mortality rate also depended on the age of the patient; only one patient under 40 (1.1%) died, whereas 19% over 40 died. Of the operated patients, four died from bleeding, three from cardiac and circulatory failures, two from pulmonary embolism, and one each from pneumonia and peritonitis. Of the conservatively treated patients, four died from bleeding and two from cardiac and circulatory failure.

Ventricular ulcers were also treated conservatively if the first bleeding could be stopped or if an operation was not possible because of advanced age or poor general condition, or when operation was refused.

Oesophageal Varicose Bleeding vs. Liver Damage

The fate of patients with acute varicose bleeding is largely dependent on the degree of liver damage;[9] therefore these patients should also be treated jointly by internist and surgeon. Most internists recommend operation if the extent of liver damage permits. Apart from the danger of bleeding to death, each successive bleeding leads to hypoxaemic damage. The portacaval shunt operation (splenorenal anastomosis) is the method of choice. The purse-string ligature and the dissection ligature of Vossschulte are rarely used today, but are still of value in cases where a portacaval shunt is not anatomically possible (thrombosis or deformities in the region of the portal vein). In this series, the number of dissection ligatures has also decreased in favour of portacaval anastomosis (Table 1).

Emergency Surgery vs Conservative Therapy

The mortality from bleeding oesophageal varices is given by Wildhirt[16] as 54%. Koncz[9] distinguishes between the emergency operation —10 days between onset of bleeding and therapy—and the interval operation. He reports a mortality of 12% in 350 shunt operations; after emergency operations, the mortality was 36% and after conservative therapy, 64%.

Between 1959 and 1968, 89 patients (18.5%) were treated for severe varicose bleeding from the oesophagus. Those operated when there was no bleeding are not included in this series. Thirty-nine patients (43.8%) were operated and 50 (56.2%) were treated conservatively; the mortality of the operated patients was 35.8%. This figure agrees with that given by Koncz. There was a mortality of 48% among the conservatively treated cases.

The cause of death in both the operated and the conservatively treated patients was due to liver failure, particularly coma of the liver, from which eight patients died after operation and 11 after conservative treatment. Ten patients treated conservatively died of bleeding as well as three patients, in spite of operation. Two conservatively treated patients died from heart and circulatory failure and one from pulmonary embolism; whereas two operated patients were lost from a pulmonary embolism and one from a dehiscence after dissection ligature.

The belief that 30-80% of the patients die from the first oesophageal bleeding was confirmed: 51% of the patients died from the first episode of bleeding, 41% from the second, 23% from the third, and 66.6% from the fourth.

Gastritis

In acute bleeding from erosive or haemorrhagic gastritis, an attempt must be made to stop the bleeding conservatively. This is possible in the majority of patients. If this fails, then a typical stomach resection, or a subtotal to total resection is carried out as recommended by most other workers (Wachsmuth, Wassner). Only Hoffmann considers operation unnecessary.

Between 1959 and 1968, 54 patients with stomach bleeding due to gastritis were treated (11.2%); 20 patients (37%) had to be operated, with a mortality of 15%. When one considers the type of bleeding, it is not remarkable that bleeding was sometimes not stopped

even after a two-thirds stomach resection. A second laparotomy and extensive resection was necessary in these cases. In spite of resection, however, one patient died from loss of blood; a second, from acute pancreatitis, and a third, from cardiac and circulatory failure. In 34 patients, the bleeding could be stopped conservatively. One of these died of pneumonia.

No diagnosis could be made in 60 patients (12.5%). This large number can be explained by the fact that the diagnosis of a bleeding ulcer or gastritis cannot always be made radiologically. In most of these cases, bleeding was probably due to ulcers and gastritis which were not recognised. In other patients, no diagnostic methods could be applied because of advanced age and poor general condition. A few patients left the hospital after cessation of bleeding without allowing a diagnosis to be made; 13.7% of this group died. Most of them were elderly and all bled to death.

Many other diseases lead to macroscopic gastrointestinal bleeding. Seventy-two patients (15%) in this series were hospitalised for severe bleeding. The diagnoses are summarised in Table 4.

Of the 481 patients 3.5% bled from a carcinoma of the stomach, 2.2% from a peptic jejunal ulcer, 1.4% from haemorrhoids, 1.2%

TABLE 4

Diagnosis of the Other Massive Gastrointestinal Haemorrhages

Carcinoma of the stomach		17
Peptic jejunal ulcer		11
Haemorrhoids		7
Carcinoma of the colon		6
Ulcerative colitis		5
Polypus of the sigmoid rectum		4
Hiatal hernia		4
Oesophageal diverticulum		2
Duodenal diverticulum		2
Stomach polypus		2
Stomach volvulus		1
Multiple gastrointestinal haemangiomas		1
Oesophagitis		1
Intestinal bleeding (allergic vasculitis)		1
Morbus Osler		1
Carcinoma of the head of the pancreas		1
Diverticulum of the small intestine		1
Neurinoma of the small intestine		1
Bleeding of an abdominal anus		1
Leiomyoma of the rectum		1
Injury due to a bougie in cardiac spasm		1
Zollinger-Ellison-syndrome		1
Total	15.0%	72

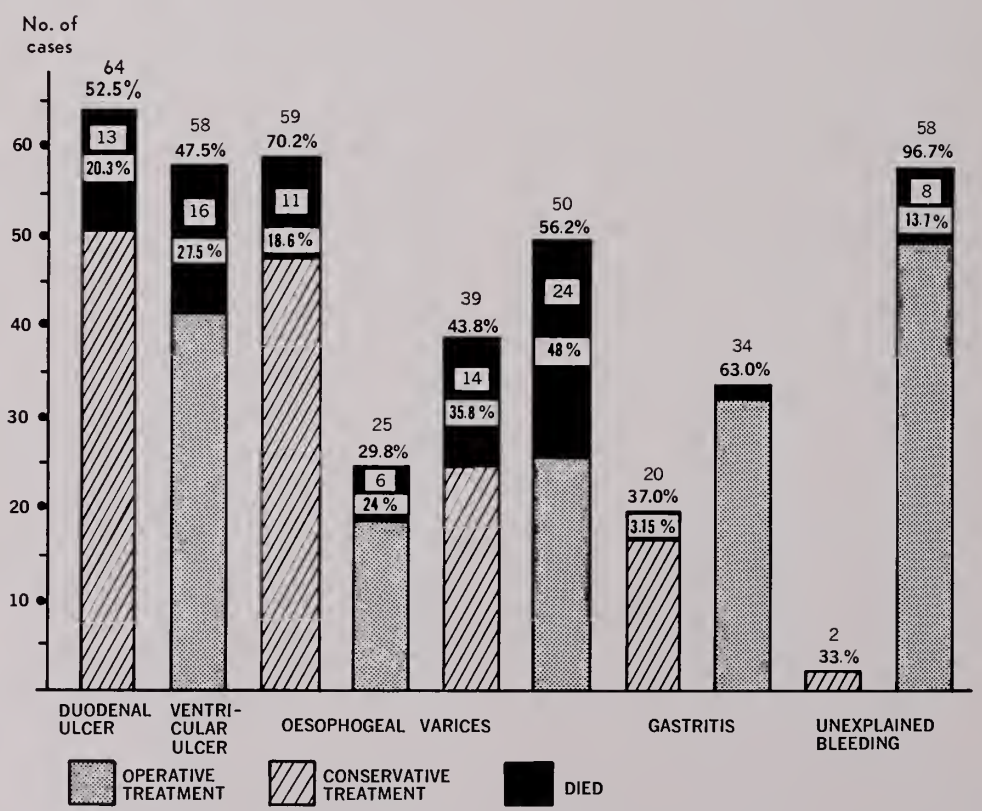


Fig. 3—Results of treatment of massive gastrointestinal bleeding.

from carcinoma of the large intestine and 1% from ulcerative colitis. All other diagnoses were under 1% (Table 2 and Figure 3).

Summary

The diagnosis, therapy and results of treatment of gastrointestinal bleeding in the literature are reported. Between 1959 and 1968, 481 cases of acute gastrointestinal bleeding from the Surgical Department of the University of Giessen are arranged according to diagnosis and evaluated. The results of operative and conservative treatment and mortality are critically examined.

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A Liberal Education

That man, I think, has had a liberal education, who has been so trained in youth that the body is the ready servant of his will, and does with ease and pleasure all the work that, as a mechanism, it is capable of; whose intellect is a clear, cold, logic engine, with all its parts of equal strength, and in smooth working order; ready, like a steam engine, to be turned to any kind of work, and spin the gossamers as well as forge the anchors of the mind; whose mind is stored with a knowledge of the great and fundamental truths of Nature and of the laws of her operations; one who, no stunted ascetic, is full of life and fire, but whose passions are trained to come to heel by a vigorous will, the servant of a tender conscience; who has learned to love all beauty, whether of Nature or of art, to hate all vileness, and to respect others as himself.

Such a one and no other, I conceive, has had a liberal education; for he is, as completely as a man can be, in harmony with Nature. He will make the best of her, and she of him. They will get on together rarely; she as his ever beneficent mother; he as her mouthpiece, her conscious self, her minister and interpreter.*

*Thomas Henry Huxley ('825-1895).

I am convinced digestion is the great secret of life.—Sydney Smith

Pollution
An Enemy of the People

Dr. Stockman: The miraculous springs that cost such a fortune to build, the whole Health Institute, is a pesthole! . . . You know the filth up in Windmill Valley? That stuff that has such a stinking smell? It comes down from the tannery up there, and the same damn poisonous mess comes right out into the blessed, miraculous water we're supposed to *cure* people with!

Hovstad: How are you so sure about this, Doctor?

Dr. Stockman: I had a suspicion about it a long time ago—last year there were too many sick cases among the visitors, typhoid and gastric disturbances. . . . The whole water system has got to be changed.

Aslaksen: The water system is very important to us little businessmen, Doctor. Kirsten Springs are becoming a gold mine for this town, especially for the property owners. . . . I don't want any wild-eyed radicalism on this thing. I've had enough of that in my time, and no good ever comes of it.

Peter Stockman: I don't suppose you have taken the trouble to consider what your proposed changes would cost?

Dr. Stockman: No, I never thought of that.

Peter Stockman: Naturally. Your little project would come to at least three hundred thousand crowns. . . . The worst thing is that it would take some two years. . . . And what do you propose we do about the springs in the meantime? Shut them up, no doubt! As soon as the rumor gets around that the water is dangerous, we won't have a visitor left. . . . Now look, I'm going to lay this out once and for all. I told you the stakes you are playing for here, and now I am going to give you an order.

Dr. Stockman: What kind of an order?

Peter Stockman: You are going to deny these rumors officially. . . . You simply say that you went into the examination of the water more thoroughly and you find that you overestimated the danger.

Dr. Stockman: My convictions come from the condition of the water. My convictions will change when the water changes, and for no other reason.

Peter Stockman: . . . Now this is our crisis. We know what this town was without our Institute. We could barely afford to keep the streets in condition. Today we're on the verge of becoming internationally known as a resort. We live or die on what the outside world thinks of us. I believe there is a line that must be drawn, and if a man decides to cross that line, we the people must finally take him by the collar and declare, "You cannot say that!"

Dr. Stockman: Answer me this! A platoon of soldiers is walking down a road toward the enemy. Every one of them is convinced he is on the right road, the safe road. But two miles ahead stands one lonely man, the outpost. He sees that the road is dangerous, that his comrades are walking into a trap. He runs back, he finds the platoon. Isn't it clear that this man must have the right to warn the majority, to argue with the majority, to fight with the majority if he believes he has the truth? Before many can know something, *one* must know it! . . .

Aslaksen: Doctor, you could have everything you want!

Dr. Stockman: Except the truth. I could have everything but that. . . . But the children are poisoned, the people are poisoned! If the only way I can be a friend of the people is to take charge of that corruption, then I am an enemy! The water is poisoned, poisoned, poisoned! That's the beginning of it and that's the end of it! . . . I'm the enemy—and now you're first going to find out what kind of enemy I am! Ring the bells, sound the alarm! The truth, the truth is out!*

*From Henrik Ibsen's "An Enemy of the People."

Percutaneous Transhepatic Cholangiography

In Diagnosis of Diseases of the Biliary Tract*

S. BAYINDIR, M.D.,† H. F. SCHIRMER, M.D.,† N. HEGER, M.D.† and R. STECKENMESSER, M.D.†

Icterus can be symptomatic for a variety of diseases. In most cases the type of icterus—haemolytic, parenchymatous, or obstructive—can be diagnosed from clinical and clinico-chemical examinations. Difficulties in diagnosis occur particularly in the differentiation of primary biliary cirrhosis, intrahepatic cholestasis and extrahepatic obstruction.[9,10,11,12,16,19] Although a differentiation between parenchymatous and obstructive icterus is possible in 85 to 90% of the cases,[10,4] localisation of the obstruction is often difficult in obstructive icterus.

An explanation of the conditions in the biliary tracts cannot be expected from routine radiological methods (oral and intravenous cholecysto-cholangiography) in icteric patients. Intravenous cholangiography is also unsuccessful in some non-icteric patients with incomplete obstruction in the region of the hepatocholedochus. Because of insufficient elimination, the contrast may not be sufficient to allow exact evaluation. This is true, for example, in some inflammatory stenoses of the papilla, in calculi in the choledochus, in stenosis of the choledochus secondary to chronic pancreatitis of the head of the pancreas, and in bilidigestive anastomoses.

In all these cases, percutaneous transhepatic cholangiography can be used for the exact clarification of the anatomo-pathological conditions of the biliary tracts.

Technique

A thin stilette, 1.1 mm in diameter and 15-17 cm in length surrounded by a polyethylene catheter, PE 160, or an even thinner stilette 0.8 mm in diameter (Figure 1) is used to puncture an intrahepatic bile duct. The point of the catheter is drawn out so that it fits the point of the stilette closely. Before puncture, the skin and sublayers are incised under local anaesthesia at the site of puncture. With the patient holding his breath, the catheter with the stilette in position is directed towards the 11th thoracic vertebra or its lower border and inserted into the liver. The process is controlled by an image intensifier with television monitor. After successful puncture, the stilette is immediately removed, and the patient is allowed to breathe superficially. The flexible catheter moves with the liver during respiration without causing any damage (Figure 2). If bile flows out of the catheter, as much as possible is sucked off before filling the bile ducts with contrast medium in order to relieve the pressure. If no bile flows from the catheter, the latter is slowly withdrawn until bile appears. If the second puncture is also unsuccessful, the plastic catheter is withdrawn during the third attempt under continuous injection of small amounts of contrast medium until the biliary duct is filled, as judged by the x-ray picture. In non-icteric patients, this method is used for

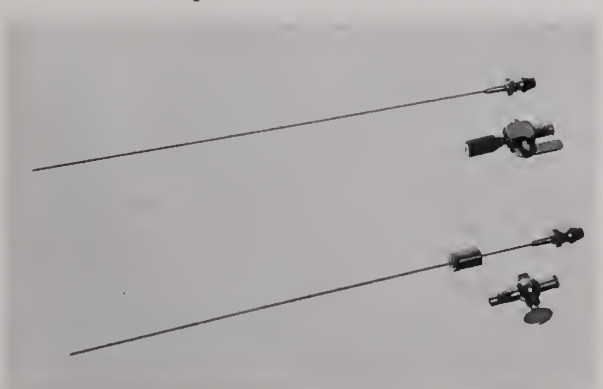


Fig. 1—Above: Stilette and polyethylene catheter with connecting piece. Below: Guide with surrounding polyethylene catheter. Next to it, a model of a connecting tap which can be unscrewed.

*See editorial, page 1117.

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the first puncture. Serial pictures are taken during the filling of the biliary tract with contrast medium (20-50 ml 30 or 60% Conray). If there is complete obstruction of the contrast medium, then films taken standing, in addition to the usual supine pictures, are necessary for an exact diagnosis.

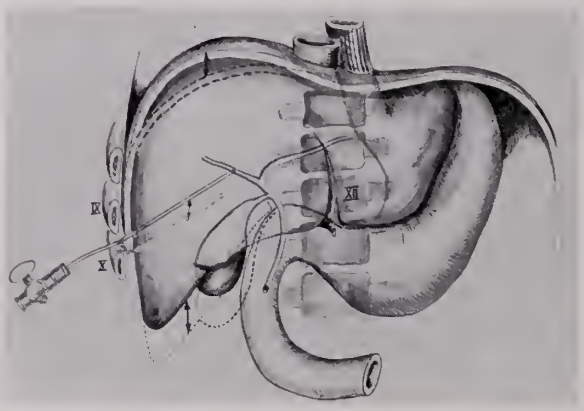


Fig. 2—(Semi-diagrammatic) shows site of puncture and direction. During inspiration, the catheter moves with the liver and diaphragm (shaded).

Indications

There is strict indication for percutaneous transhepatic cholangiography in 1. obstructive icterus, 2. unexplained icterus, 3. non-icteric, previously operated patients with or without bilidigestive anastomoses who have non-characteristic upper abdominal complaints and symptoms which cannot be attributed to the gastrointestinal tract, and in whom the intravenous cholecysto-cholangiography is negative.

The indication is regarded as relative when cholecysto-cholangiography is negative or cannot be safely evaluated because of weak contrast in patients with symptoms of unknown origin who have not previously been operated on the biliary tract.

Contraindications

1. Hypersensitivity to contrast medium. 2. Tendency to bleeding (minimal Quick value between 60 and 70%). 3. Echinococcus of the liver. 4. Liver abscess. 5. Poor general condition in patients who cannot withstand laparotomy, since in such cases, the radiological diagnosis does not lead to therapeutic measures.

Clinical Material

One hundred and sixty-six patients have been examined by percutaneous transhepatic cholangiography; 139 had an icterus and 27 were anicteric; 44 had already undergone operation on the biliary tract once or several times previously. Of these patients, 27 had an icterus and 17 were anicteric. Table 1 compares the radiological and final diagnoses which were obtained by operation, liver biopsy, autopsy and other examinations.

Calculi in the biliary tracts were diagnosed 53 times radiologically but were found in 55 cases on operation. The two non-diagnosed patients are listed under the unsuccessful punctures in the Table; in both patients it was not possible to puncture the intrahepatic bile ducts. In one patient the icterus had begun only five to six days previously, so that the bile ducts were not yet distended; in the second patient, the puncture technique was imperfect. In the

TABLE I

Comparison of the Radiological and Final Diagnosis in 166 Percutaneous Transhepatic Cholangiographies

	Radiological Diagnoses		Final Diagnoses	
Calculi in the biliary tract	53	(+2)	55	33.1%
Stenosis of the hepatocholedochus due to chronic inflammatory processes (sphincter sclerosis, pancreatitis of the head of the pancreas)	10	(—1)	9	5.4%
Cholestasis due to scarring after operation and operative injury	12		12	7.2%
Tumours of the gallbladder and biliary tract	33		33	19.9%
Tumours of the pancreas	24		24	14.5%
Obstruction of the hepatocholedochus due to metastases	4		4	2.4%
No obstruction of the biliary tract	16	(+1)	29	17.5%
Puncture unsuccessful	14	(—2)		
	166		166	100.0%

next group (stenosis of the hepatocholedochus due to chronic inflammatory processes), there were 10 cases diagnosed radiologically as compared to nine cases of stenosis of the extrahepatic ducts found on operation. In one patient in this group, a stenosing process in the region of the papilla was diagnosed radiographically but not confirmed on operation. It is assumed in this case that the calculus had already been discharged as the icterus regressed preoperatively after the percutaneous transhepatic cholangiography. Small calculi were found in the gallbladder intraoperatively 10 days after percutaneous transhepatic cholangiography and the bile ducts were free. The numbers in groups 3 to 6 correspond to each other. Differences were found in groups 7 and 8. The case mentioned above must be included in the group with free passage of the biliary tract. The two patients with obstructions due to calculi belong to the group of unsuccessful punctures. In the remaining 12 patients, in whom puncture was not successful, no obstruction was found on operation.

Calculi in the Biliary Tracts
(55 patients, 33.1%)

Forty-one patients had a marked icterus and 13 were anicteric. Puncture and filling of the bile ducts, as well as an unequivocal diagnosis, could be made in 53 cases. The bile ducts could not be punctured in two patients with icterus (see above).

The diagnosis of calculi is rarely difficult. Relatively smoothly bordered, triangular or spherical defects in the filling depending on the shape of the stone are observed (Figure 3). The complete obstruction of the main bile duct by a stone can be recognised by the piscine* like shape of the calculus, as well as by cranially convex bordered interruptions in the column of contrast medium.

Stenosis of the Extrahepatic Biliary Ducts
(9 patients, 5.4%)

This may be due to chronic inflammatory processes. Six had an icterus and the remaining three were anicteric. Puncture and filling of the bile ducts were successful in all cases and proved the presence of papillary stenosis.

*See Test Your Word Score, page 1131.



Fig. 3—Fifty-nine-year-old ♂ icteric patient. A stone is situated directly above the papilla and further calculi can be seen in the middle of the choledochus and cystic ducts. Cystic obstruction.



Fig. 4—Sixty-six-year-old ♀ icteric patient. Marked distension of the intra- and extrahepatic bile ducts in sclerosis of the sphincter.

All patients showed retarded drainage of the contrast medium into the duodenum due to the narrowing of the papillary and suprapapillary section of the choledochus with slight or marked distension of the hepatocholedochus proximal to the stenosis. In papillary sclerosis the stenosed section can be short or extended, or can show kinking and step-formation (Figure 4).

Cholestasis due to Scarring following Operation or Operative Injury (12 patients—10 icteric and 2 anicteric = 7.2% of all patients)

Strictures of the biliary tract after cholecystectomy and choledochotomy due to postoperative inflammatory changes are rare and are usually due to operative injury.[7,5,15] These were found to have cholestasis due to scarring after previous operations: four cholecystectomies with choledochus revision, three hepaticojejunostomies, and two hepaticoduodenostomies (Figure 5).



Fig. 5—Forty-six-year-old ♂ icteric patient. Condition after cholecystectomy. Complete blockage of the common hepatic duct below the bifurcation due to cicatricial stenosis.

Carcinoma of the Gallbladder and Bile Ducts (33 patients, 19.9%)

Complete or incomplete obstruction characteristic for tumours of the gallbladder or bile ducts was found. All patients had a marked icterus. In 25 cases the malignant tumour originated in the gallbladder or bile ducts and in eight cases in the duodenal papilla. The biliary tract could be punctured in all cases. An obstruction of the common hepatic duct extending from below the bifurcation to the transition into the choledochus duct was characteristic in most of these tumours. Radiological differentiation between carcinoma of the gallbladder and the bile ducts was usually impossible, as the obstructions are smoothly contoured or irregularly serrated (Figure 6). Tumours of the papilla could be recognised by their localisation and from the shape of the obstruction, as in the other tumours. However, the differential diagnosis between tumours and sclerosis of the papilla can be difficult.



Fig. 6—Sixty-four-year-old ♀ icteric patient. Severe dilation of the intrahepatic ducts due to obstruction below the bifurcation in carcinoma of the gallbladder or biliary tract.

Tumours of the Pancreas (24 patients, 14.5%)

The obstruction was found in most cases in the pancreatic or retroduodenal section of the choledochus (upper edge of the pancreas),



Fig. 7.—Fifty-six-year-old ♂ icteric patient. Severe dilation of the choledochus duct. The obstruction is smoothly bordered in the intrahepatic section. Carcinoma of the pancreas.



Fig. 8—Fifty-six-year-old ♀ icteric patient. Condition after cholecystectomy. Demonstration of intra- and extrahepatic biliary tract. Long stump of the cystic duct. Treatment conservative.

rarely in the region of the papilla or common hepatic duct. When the obstruction was incomplete, there was marked stenosis of the choledochus with or without irregularities in the contour. In the conic form, the possibility of pancreatitis of the head of the pancreas must be considered in the differential diagnosis. Botuliform, smoothly bordered contours are found when there is complete obstruction (Figure 7).

Obstruction due to Metastases of the Extrahepatic Bile Ducts (4 patients, 2.4%)

If icterus occurs in a patient known to have a primary tumour, the possibility of generalised metastases in the liver or mechanical blockage of the biliary tract due to metastases, or both factors, must be considered. The decision as to the cause of the icterus is important from a therapeutic point of view. Surgery does not come into question in liver metastases, but can be considered as a palliative measure when the extrahepatic bile ducts are occluded. A bilidigestive anastomosis could be performed in two out of the four patients; but in the remaining two a palliative operation was no longer possible.

Free Drainage of the Bile Ducts (29 patients, 17.5%)

Puncture of the intrahepatic bile ducts was successful in 17 cases. The patency of the larger intrahepatic gall ducts and of the extrahepatic ducts could be demonstrated by filling with contrast medium (Figure 8). In 12 patients in whom puncture was unsuccessful, it was concluded from the negative results that there was no obstruction in the surgical sense which had led to the distension of the intrahepatic branches. The final diagnoses after laparotomy, autopsy, histology and later examinations were: lymphogranulomatosis of the liver (1), reticulosis (1), metastases in the liver (2), chronic hepatitis with acute flare-up (1), morbus Meulengracht (1), questionable hepatitis (1), intrahepatic cholestasis (1), chronic recurrent cholangitis (2), questionable cholangitis (1).

The Significance of Percutaneous Transhepatic Cholangiography in Anicteric Patients

Twenty-seven out of 166 patients were anicteric. Puncture of the intrahepatic bile ducts was successful in 24 and unsuccessful in three. Seventeen of the 27 patients had already undergone operations on the biliary tract. In these patients. percutaneous transhepatic cholangiography revealed the following diagnoses: obstruction due to calculi (9), sclerosis of the sphincter (2), cicatricial cholestasis of the choledochus duct after operative injury (1), stenosis of the bilidigestive anastomsis (1), patent bile ducts (2), unsuccessful puncture with patent bile ducts (2) = 17 patients.

The diagnosis of the remaining anicteric cases were: incomplete obstruction due to calculi (3), patent bile ducts—three with stones in the gallbladder (4), pancreatitis of the head of the pancreas with calcification (1), unsuccessful puncture—biliary tract operatively free, cholecystitis (1).

These numbers emphasize the significance of percutaneous transhepatic cholangiography in anicteric patients with a negative cholecystocholangiography before they are operated.

Complications

Out of 166 patients, 54 were examined after percutaneous transhepatic cholangiography independent of operation. On the basis of the percutaneous transhepatic cholangiography results, 25 of them were not operated and 29 only several days or weeks later.

Fever (12 of 54 patients)

An increase of body temperature of 1-2° occurred two to five hours after percutaneous transhepatic cholangiography, but temperature returned to normal within 12 to 48 hours under the administration of antibiotics. This phenomenon is regarded as a reactivation of an existing infection of the biliary tract and is considered a mild, insignificant complication.

Bile (2 patients)

In two patients operated on the day of examination, large amounts of bile (200-300 ml) were found in the abdomen. In both cases there was a mistake in puncture technique; in one the neck of the gallbladder had been punctured and in the other, the stilette had slipped over the lower edge of the liver puncturing a gall duct, out of which bile exuded into the abdominal cavity. If the operation had not been performed after percutaneous transhepatic cholangiography, a bilious peritonitis could have resulted in both cases. No significant amounts of blood were ever found in the abdominal cavity on operation.

Blood (1 patient)

In one anicteric patient who had had a previous operation on the biliary tract, and who was not operated after percutaneous transhepatic cholangiography, there was a prolonged fall in blood pressure with bradycardia and increase in temperature which lasted several hours. However, the blood pressure could be maintained and stabilised by infusion and injection of noradrenalin; normal blood pressure and temperature were recorded 12 hours later. This complication was interpreted as a local peritoneal irritation with reflex dilation of the



Fig. 9—Fifty-eight-year-old ♀ anicteric patient. Condition after cholecystectomy and choledochoduodenostomy. Partial stenosis of the anastomosis. Calculi in the distal choledochus.

visceral blood vessels. In order to avoid such complications, an infusion is recommended after percutaneous transhepatic cholangiography in all patients who are not operated immediately (Figure 9).

The three cases described above were the only serious complications that occurred in this series of 166 patients (= 1.8%).

Discussion and Conclusions

In cases of obstructive icterus, percutaneous transhepatic cholangiography is of value in determining the causes and localisation of the obstruction. This is important for the operation. In cases of unexplained icterus, percutaneous transhepatic cholangiography can contribute significantly to the diagnosis. If the bile ducts can be punctured and demonstrated, then the diagnosis is certain when considered in conjunction with clinical and clinico-chemical findings. If the intrahepatic bile ducts cannot be punctured, then it is very probable that there is no obstructive icterus with dilation of the intrahepatic ducts in the surgical sense, and liver biopsy can be performed without danger of a resulting bilious peritonitis (Figure 8). The same is true for patent, non-dilated bile ducts; laparotomy can be avoided or postponed in these cases. Cholecysto-cholangiography under laparoscopy cannot replace percutaneous transhepatic cholangiography for the following reasons: the spiral valve can hinder the transfer of contrast medium into the choledochus duct even when the cystic duct is free. Demonstration of the gallbladder alone is of secondary importance in the diagnosis of obstructive icterus. In many cases of obstruction due to calculi, the cystic duct is also obstructed. Obstruction above the point of entry of the cystic duct can lead, therefore, to false conclusions. The method cannot be used after cholecystectomy and is difficult when the gallbladder has shrunk, or there are extensive adhesions in the upper abdomen. The following numbers show that percutaneous transhepatic cholangiography is also indicated in anicteric patients, particularly those who have already been operated. The puncture was successful in 24 out of 27 patients and pathological results were found in 21 of them. There is no absolute necessity for immediate operation after percutaneous transhepatic cholangiography, even if obstruction is found. The patients should, however, remain under close clinical observation.

Summary

One hundred and sixty-six patients (139 icteric and 27 anicteric) were examined by percutaneous transhepatic cholangiography. There were 137 cases of complete or incomplete disturbances of flow in the region of the hepatocholedochus, and puncture and subsequent filling with contrast medium were successful in 135 (98.5%). An intrahepatic bile duct could be punctured in 17 out of 29 cases with a patent biliary tract (59%). The puncture was successful in 24 out of 27 anicteric patients (89%) with incompletely blocked or patent bile ducts. One hundred and twelve patients were operated immediately after percutaneous transhepatic cholangiography and 29 patients several days or weeks later; 25 were not operated.

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8-20. May be secured from the author or the reprints.

Infection

If I had my way I'd make health catching instead of disease.—Robert Ingersoll

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Side Effects: Dryness of the mouth, mydriasis, hesitancy of urination; less commonly extrapyramidal (restlessness, dystonia and signs of pseudoparkinsonism such as muscular rigidity, fixed facies, tremor, ataxia, festinant gait and drooling), parasympatholytic (blurred vision, xerostomia, hypotension, nasal congestion and constipation) and curare-like (loss of control of voluntary muscles, particularly the muscles of respiration) reactions. Rarely, leukopenia or allergic purpura. A generalized erythematous skin reaction may occur. Side effects characteristic of phenothiazines such as grand mal convulsions, altered cerebrospinal proteins, cerebral edema, potentiation of the effects of atropine, heat or phosphorus insecticides, autonomic reactions, endocrine disturbances, reversed epinephrine effect, hyperpyrexia or pigmentary retinopathy may theoretically occur but have not been reported with Dartal. Severe hypotension following recommended doses occurs more commonly in patients who are also afflicted by other medical disorders such as mitral insufficiency or pheochromocytoma, and particular attention should be paid to such a possibility although this has not been observed with Dartal.

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Warning: May be habit-forming.

For *Indications*, *Contraindications*, *Precautions*, *Side Effects* and *Dosage* see Pro-Banthine. In addition, phenobarbital should be administered with caution to patients with liver disease, mental disturbances or a significant degree of hypoxia.

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For *Indications*, *Contraindications*, *Precautions* and *Side Effects* see Pro-Banthine.

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Dosage: The recommended initial dosage is one tablet in the morning and one at night.

084

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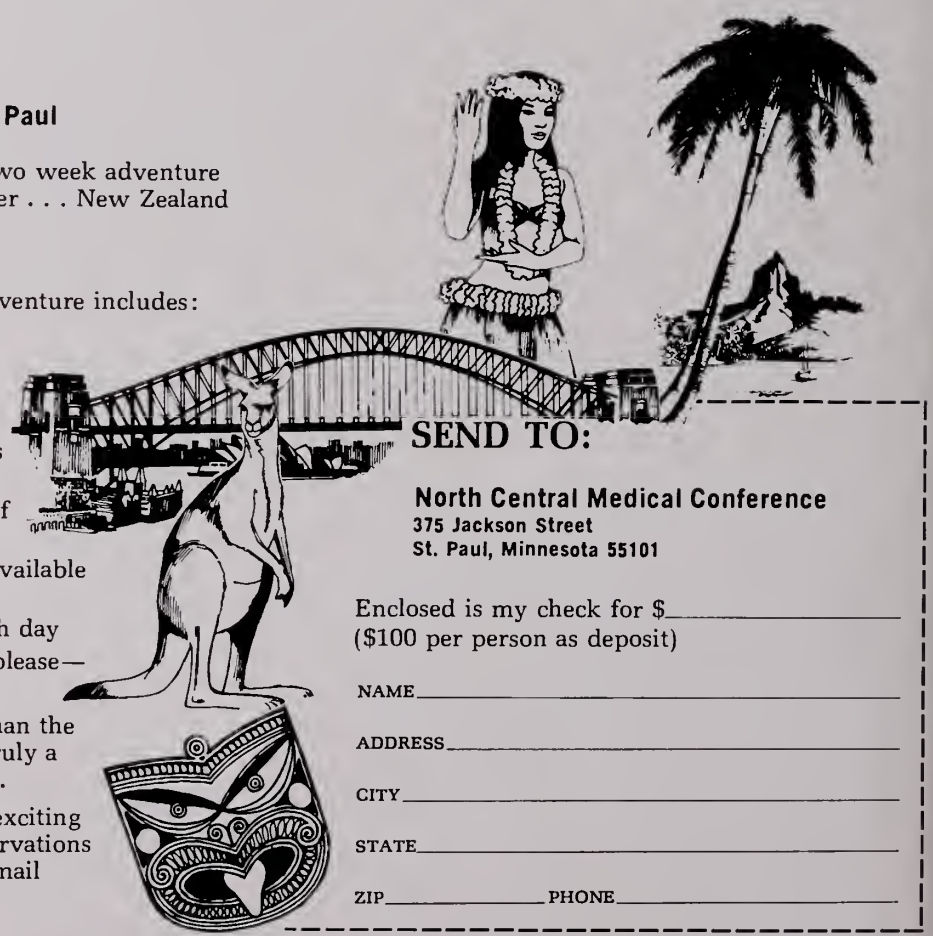
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Editorials

Percutaneous Transhepatic Cholangiography

PERCUTANEOUS TRANSHEPATIC cholangiography can give important diagnostic information and is a valuable technical aid for the surgeon who operates on a patient with jaundice or with biliary obstructive symptoms. The article, "The Significance of Percutaneous Transhepatic Cholangiography in Diagnosis of Diseases of the Biliary Tract" by Bayindir and associates, in this issue,* emphasizes the value of this technic.

At the Cleveland Clinic, during the last six years, we have had an almost equal experience with percutaneous transhepatic cholangiography. Our present indications for the procedure are: 1) to establish the presence or absence of obstruction in puzzling cases of jaundice; 2) to identify the site of obstruction and to help determine the nature of the lesion; and 3) to investigate the cause of biliary symptoms which occur after prior cholecystectomy, especially when benign strictures or recurrent common bile duct stones are suspected, in patients in whom intravenous cholangiography does not adequately visualize the biliary system. During the last three to four years, our radiologists have been performing the percutaneous transhepatic cholangiograms in the Radiology Department, using local anesthesia, the morning of the day that the operative exploration of the biliary system is scheduled. The procedure is performed under fluoroscopic control, much as described by Doctor Bayindir and his associates. With prompt operative exploration and biliary decompression within two to four hours after the diagnostic procedure in all patients who have an obstructed biliary system, there have been no significant complications from the use of percutaneous transhepatic cholangiography. We do not delay operation or undertake catheter decompression of the biliary system as has been advocated by other authors.

When a dilated, obstructed biliary system is entered, the cholangiogram establishes the fact that this is obstructive jaundice and provides visual identification for the surgeon (and for the record) of the point of obstruction; and all patients are operated upon within two to four hours. When a non-dilated, or normal biliary system is identified by percutaneous transhepatic cholangiography and there is a free flow of dye into the duodenum, we cancel the planned operative exploration of the biliary system. A needle biopsy of the liver is obtained on such patients, to confirm the presumptive diagnosis of hepatitis or other primary liver disorder as the cause of the jaundice. Operation is thus avoided when a normal cholangiogram is obtained.

In about 15 percent of our patients, percutaneous transhepatic cholangiography is unsuccessful. The failure rate naturally depends on

*See page 1107.

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the skill and experience of the man performing the needle puncture of the liver. We arbitrarily limit ourselves to five attempts to introduce the needle into the biliary system. One is tempted to conclude when no dye enters the biliary system that it is not obstructed; but in our experience this may be a fallacious assumption and potentially dangerous to the patient. We therefore proceed with operative exploration of every patient in whom percutaneous transhepatic cholangiography has not been successful. In a significant number of such patients we have found an obstructed, dilated biliary system which had simply eluded the needle tip.

Percutaneous transhepatic cholangiography is a valuable diagnostic study when it shows a dilated or a non-dilated biliary system. When the test is not successful and the biliary system cannot be entered, it should be disregarded. In the latter circumstance, we advise operative exploration of the biliary system and intra-operative cholangiography to diagnose the exact cause of the jaundice.

Robert E. Hermann, M.D.*
Stanley O. Hoerr, M.D.*
Cleveland, Ohio

*The Cleveland Clinic Foundation.

Surgical Treatment of Metastases of Carcinoma of the Breast

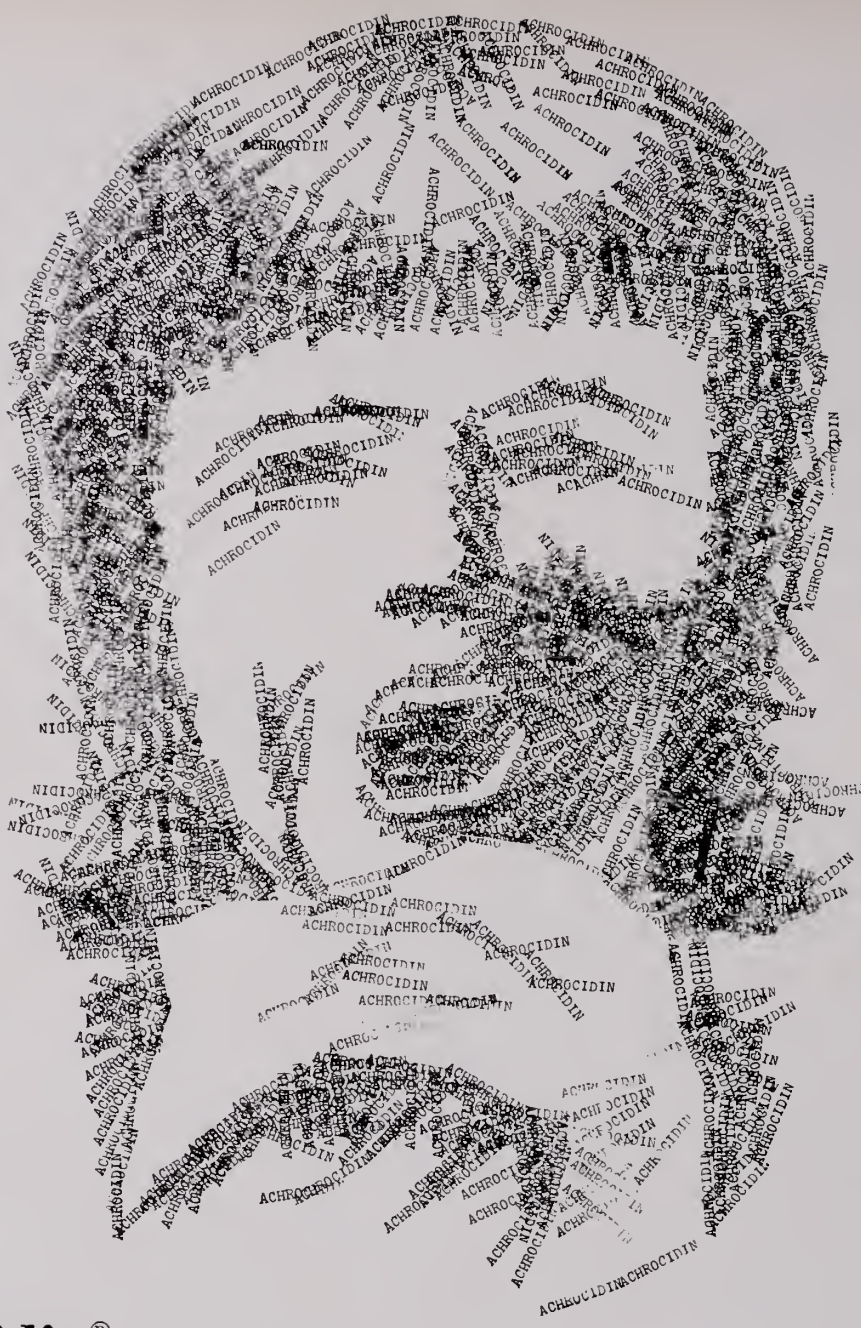
Doctor Schoen* in his report with a rather large experience has emphasized the need to individualize patients suffering from extension of a primary carcinoma of the breast. Recent studies by the author with scanning of the bones in patients who present themselves with primary operable cancer of the breast, have shown that a significant number of these patients have evidence of metastases at the time when they first present themselves. Nevertheless, the best treatment even under these circumstances is to perform a radical mastectomy, the reason for this being that patients, although they have metastases to bone, will live many, many years. The knowledge that patients who have dissemination of their cancer arising from a primary in the breast will live for prolonged periods, focuses on the need to perform radical surgical procedures where indicated. The fact that of 23 patients with metastases extensive resections could be performed in only three of Doctor Schoen's patients, indicates the relative infrequency with which one is called upon to perform these radical procedures.

Prudente† has performed radical interscapulothoracic mammary amputations for patients with breast cancer that has been fixed to the axilla. Most of these patients have lived for many years, and this editor has performed a similar procedure several times with gratifying results. The indications, however, must be clearly defined, and it is only the clinician who has to "live with the patient," who can make such a decision.

The procedure of osteosynthesis which Doctor Schoen performed in eight patients is an extremely important operative procedure in patients with impending or obvious fractures of their femur. Many of these patients are old, and to be bedridden for prolonged periods is almost tantamount to signing a death warrant. The practice of internal nailing, or the more recent practice of putting in a prosthetic joint, is a surgical procedure which is very well tolerated by the patient and permits early ambulation. It is a procedure which should be considered for every patient with metastases to the upper femur.

On the other hand, the practice of removing solitary metastases from the brain, lungs or liver, etc., presents an entirely different problem. Only in an occasional case, as discussed in the paper, is a metastatic deposit in the brain to be considered for surgical excision. I do not believe it is ever warranted for metastases to the liver or to the lung. Unlike fibrosarcoma

*See page 1087.
†Ariel, I. M., and Pack, G. T.: The Treatment of Cancer and Allied Diseases. Vol. 5, 2nd Ed.



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Contraindications: Hypersensitivity to any component.

Warning: In renal impairment, since liver toxicity is possible, lower doses are indicated; during prolonged therapy consider serum level determinations. Photodynamic reaction to sunlight may occur in hypersensitive persons. Photosensitive individuals should avoid exposure; discontinue treatment if skin discomfort occurs.

Precautions: Drowsiness, anorexia, slight gastric distress can occur. In excessive drowsiness, consider longer dosage intervals. Persons on full dosage should not operate vehicles. Nonsusceptible organisms may overgrow; treat superinfection appropriately. Treat beta-hemolytic streptococcal infections at least 10 days to help prevent rheumatic fever or acute glomerulonephritis. Tetracycline may form a stable calcium complex in bone-forming tissue and may cause dental staining during tooth development (last half of pregnancy, neonatal period, infancy, early childhood).

Adverse Reactions: *Gastrointestinal*—anorexia, nausea, vomiting, diarrhea, stomatitis, glossitis, enterocolitis, pruritus ani. *Skin*—maculopapular and erythematous rashes; exfoliative dermatitis; photosensitivity; onycholysis, nail discoloration. *Kidney*—dose-related rise in BUN. *Hypersensitivity reactions*—urticaria, angioneurotic edema, anaphylaxis. *Intracranial*—bulging fontanels in young infants. *Teeth*—yellow-brown staining; enamel hypoplasia. *Blood*—anemia, thrombocytopenic purpura, neutropenia, eosinophilia. *Liver*—cholestasis at high dosage.

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or clear cell carcinoma of the kidney where solitary metastases to the lung can be removed with impunity and give excellent results, metastases from breast cancer to soft tissue organs are seldom candidates for surgical excision.

In cases of carcinoma of the breast, solitary metastases as such apparently never exist; in practically every instance they are a manifestation of a generalized spread. The fact that Doctor Schoen found no indication to perform resection of metastases to lung and liver and only one case where metastases to the brain was surgically excised, emphasizes this point.

Irving M. Ariel, M.D., F.A.C.S.
New York, New York

Percutaneous Catheter-Arteriographies Using the Seldinger Technique*

I BELIEVE THIS to be an important contribution to the literature. While there have been a number of previous articles dealing with complications of percutaneous angiography, most of these have been either a very small series where statistics can be badly skewed by virtue of the small number of patients involved, or collected series, where variations in the skill of the angiographers make the conclusions suspect.

The authors document well the age group studied and tabulate well the regions studied. The article would be somewhat more complete if the clinical indications for the angiogram were listed.

I would agree that the complication rate of 0.8% is a very acceptable risk and compares closely with my personal experience.

Thomas F. Meaney, M.D.†
Cleveland, Ohio

*See page 1093.

†Chairman, Division of Radiology, Cleveland Clinic, Cleveland, Ohio.

Which?

One speaker squelched a "hissing" heckler by this direct method: "There are only three things that hiss—a goose, a snake, and a fool. Identify yourself!"—M. Dale Baughman: Treasury of Stories.

Never was a good work done without much trouble.—Culinary Almanac.

The Orphan

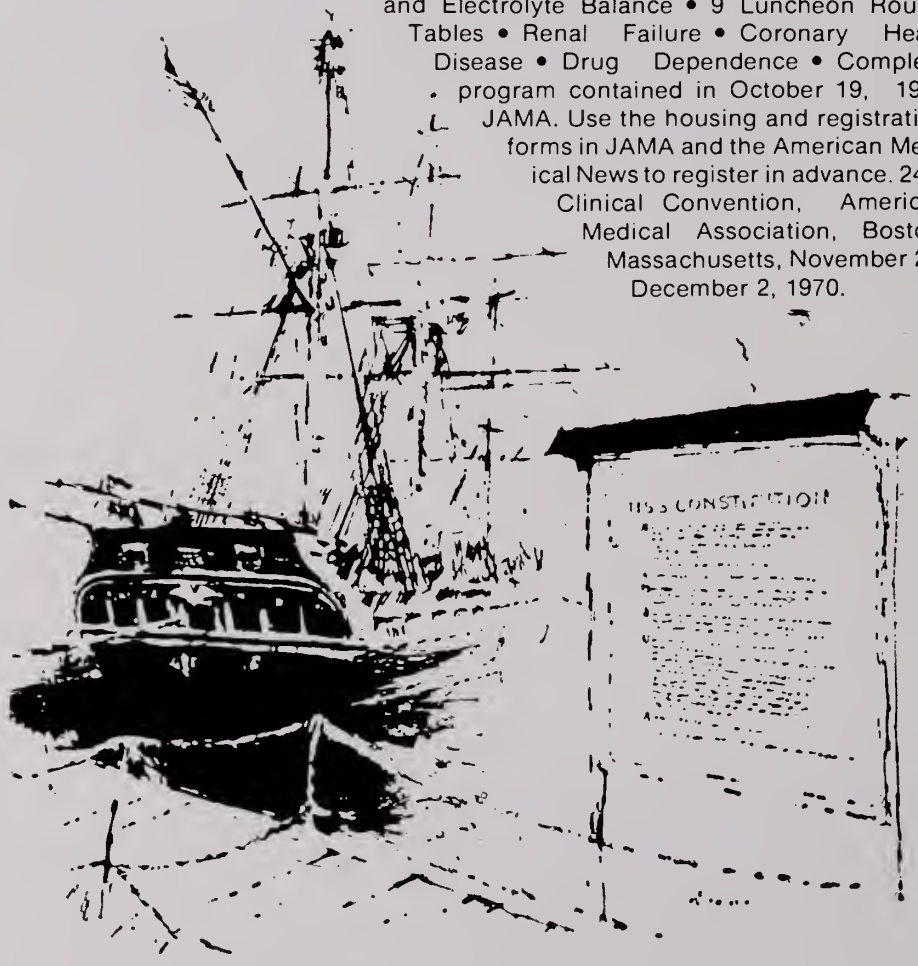
It is not surprising to find that Mohammed, himself an orphan, was deeply concerned with the protection of children who had lost their parents:

"And give the orphans when they come to age their substance; and render them not in exchange bad for good; and devour not their substance, by adding it to your own substance; for this is a great sin. And if ye fear that ye shall not act with equality toward orphans of the female sex, take in marriage of such other women as please you, two, or three, or four, and not more. But if ye fear that ye cannot act equitably towards so many, marry only one, or the slaves which ye shall have acquired. This will be easier, that ye swerve not from righteousness. And give women their dowry freely; but if they voluntarily remit unto you any part of it, enjoy it with satisfaction and advantage. And give not unto those who are weak of understanding the substance which GOD hath appointed you to preserve for them; but maintain them thereout, and clothe them, and speak kindly unto them."*

*Arabic Pediatrics, from History of Medicine, C. C. Mettler and F. A. Mettler, p. 705.

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Adverse Reactions: Rarely severe enough to require discontinuation of therapy, unpleasant symptoms with diethylpropion hydrochloride have been reported to occur in relatively low incidence. As is characteristic of sympathomimetic agents, it may occasionally cause CNS effects such as insomnia, nervousness, dizziness, anxiety, and jitteriness. In contrast, CNS depression has been reported. In a few epileptics an increase in convulsive episodes has been reported. Sympathomimetic cardiovascular effects reported include ones such as tachycardia, precordial pain, arrhythmia, palpitation, and increased blood pressure. One published report described T-wave changes in the ECG of a healthy young male after ingestion of diethylpropion hydrochloride; this was an isolated experience, which has not been reported by others. Allergic phenomena reported include such conditions as rash, urticaria, ecchymosis, and erythema. Gastrointestinal effects such as diarrhea, constipation, nausea, vomiting, and abdominal discomfort have been reported. Specific reports on the hematopoietic system include two each of bone marrow depression, agranulocytosis, and leukopenia. A variety of miscellaneous adverse reactions have been reported by physicians. These include complaints such as dry mouth, headache, dyspnea, menstrual upset, hair loss, muscle pain, decreased libido, dysuria, and polyuria.

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Exchange Transfusions in Hepatic Failure*

A HEPATECTOMIZED DOG connected to a normal dog by cross-circulation can be kept alive and alert. Toxic substances that accumulate are removed by the normal dog's liver; or essential metabolites that may be needed are supplied. In exchange transfusion essentially the same process occurs, except that the connection between the two animals is interrupted and the normal animal's blood is preserved in a bag or a bottle before it is infused into the recipient. Thus, if uncomplicated cross-circulation works, and it does, one should expect exchange transfusion to work also. When exchange transfusion fails, the failure is presumably due to insufficient exchange or to the inability of the damaged liver to recover. Many factors, mostly unknown, influence the regeneration of damaged liver tissue.

All of the clinical observations have been uncontrolled, whether or not the patient recovered. Despite the lack of control, one cannot fail to be impressed when, temporarily in direct relation to an exchange transfusion, a comatose patient wakes up, even though transiently. Repetition of the same process several times in the same patient, as has been reported, decreases the likelihood that the temporary improvement was a chance phenomenon. These clinical observations have been supported by controlled observations of Trey and colleagues in monkeys and of Turcotte and coworkers in dogs. Their experiments have demonstrated that exchange transfusions will reverse the phenomena of hepatic coma temporarily and will prolong survival, but must be applied repeatedly. Unless hepatic regeneration occurs, death is inevitable.

Obviously there is no purpose in applying exchange transfusion in clinical circumstances where there is no reason to believe that spontaneous hepatic regeneration will occur, as in advanced cases of cirrhosis. The important area of potential application is viral hepatitis with extensive hepatic destruction and coma. In man the statistics of recovery from episodes of hepatic coma associated with viral hepatitis are poor. Some cases of viral hepatitis with coma recover spontaneously. With data presently available, one cannot say that a significantly larger proportion of those who have been treated with exchange transfusion recover, even though the coma in individual patients has improved temporarily. We are unable to predict which patient will regenerate liver tissue and which will not. If we had a procedure for initiating, stimulating and controlling hepatic regeneration, we might hope for greater benefits from exchange transfusion, which could delay death until liver regeneration of sufficient proportions had occurred. For the present this is beyond us, and the long-term benefits of exchange transfusion are dubious.

Leslie Zieve, M.D.
Minneapolis, Minnesota

*Lindall, Arnold W.; Mason, Donald and Schultz, Alvin L.: Hepatic Coma in Pregnancy—Treated with Exchange Transfusion, Minnesota Med 1737, 1969.

Perseverance

I recall the story of a man in my home town of Bloomington who was interviewed by a newspaper reporter on his one hundredth anniversary. After congratulating the old gentleman on his anniversary, the reporter asked him a few questions: To what do you attribute your longevity? The centenarian thought for a moment and, holding up his hand and ticking off the items on his fingers, began: "I never smoked, I never drank liquor, and I never overate; and I always rise at six in the morning." To that the reporter remarked: "I had an uncle who acted the same way but he only lived to be eighty. How do you account for that?" "He didn't keep it up long enough," came the reply. —Adlai Stevenson

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Feasibility Study

On Saturday morning I dutifully attended the Surgical Section Meeting at the hospital. The entire surgical activities of one month were thoroughly discussed. The dull statistics were frequently interrupted by those who had personal knowledge of a case, to give additional information. When the discussion and exchange of experiences flowed freely within the group, a fair amount of teaching took place; when it came to the report of death cases, there were no holds barred and each case was objectively evaluated. I left the meeting convinced that we have within our hospital well-functioning controls as good and thorough as we are capable of devising.

Obviously, if this is so in one section of one hospital, it does not necessarily apply to all sections of all hospitals in our area.

Three county medical societies within our metropolitan area are now introducing a plan of medical control known as "the foundation." It is hoped that this new venture—supported by the insurance companies—will eliminate inaccuracy, ensure high-quality medical care and guarantee fair fees and payments. I am optimistic about it.

My indignation, however, was aroused when several days ago I received a letter from the Minnesota State Medical Association, signed by the Medical Director of the Feasibility Study of Quality Control of Medical Care, which urged me to participate in a Peer Review* Feasibility Study. Attached to this letter were five questionnaires to be used for the evaluation of charts. I was informed that each reviewer would be given ten charts to evaluate, for which one hour was allotted. This appears to be unreasonable, as it took me more than six minutes to read and understand the guidelines and the complicated forms which were designed for translation into computer language. A review of ten cases in one hour would be worthless.

I fail to see how a review of this type can possibly go deeper or do better than a case review by qualified physicians within their own hospital.

H. W. Heupel, M.D.
Minneapolis, Minnesota

*Editor's Note: *peer review—bureaucratese for a man-to-man fellowship and evaluation.*

Continuing Education

The beautiful edition of MINNESOTA MEDICINE has just recently arrived. I am again impressed with the high quality of this journal and with the excellence of the papers which it contains. I invariably find them informative and stimulating and a great help in my continuing medical education.

(Continued to Page 1131)

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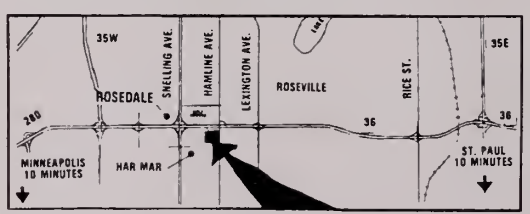
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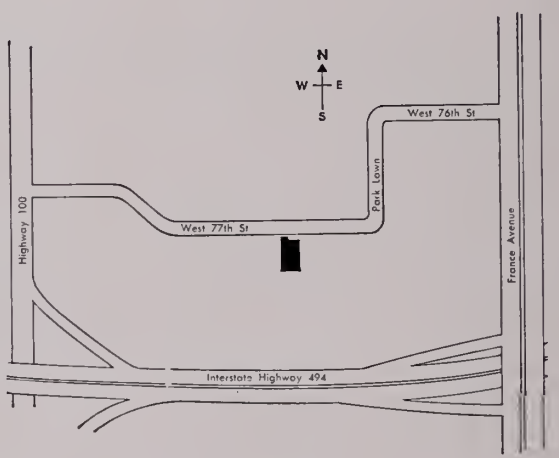
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(Continued from Page 1127)

The state of Minnesota is fortunate in having several outstanding medical centers and an abundance of highly qualified physicians practicing throughout the state. It is generally thought that the quality of medicine practiced throughout Minnesota is superior to that obtainable in most areas. It is fitting that the Minnesota State Medical Association should provide a journal which reflects the quality of medicine as practiced in Minnesota. We are indebted to you and to your staff for providing us with such a journal.

Readers of MINNESOTA MEDICINE and members of the Minnesota State Medical Association may not be aware that MINNESOTA MEDICINE has been judged the best of the state medical association journals. I hope that this high standard can be maintained and that MINNESOTA MEDICINE will always be a model for other state journals. It is obvious that to accomplish this it will be necessary to spend more money each year.

The subscription price to MINNESOTA MEDICINE and the sum allocated to MINNESOTA MEDICINE by the state association seem ridiculously low. As far as I can tell, MINNESOTA MEDICINE is the average doctor's only tangible evidence of the existence of the State Medical Association and it is by far the most important connection with the State Medical Association. I suggest to the governing body of our state association that MINNESOTA MEDICINE be given an almost unlimited budget and that the budget for useless lobbying be eliminated.

Again I want to commend you for the excellent job you have done in making MINNESOTA MEDICINE what it is today, and I congratulate you and your staff on the national recognition which you have received.

H. B. Neel, M.D.
Albert Lea, Minnesota

Test Your Word Score

Homologous graft—*same species* (Page 1077).

Isologous graft—*a homograft between highly inbred strains* (Page 1077).

Dermatitides—*plural for dermatitis* (Page 1083).

Anamnesis—*detailed history—recollection of the past* (Page 1099).

Piscine—*fish-like* (Page 1109).

Catamnesis—*medical history following the onset of illness* (Page 1138).

Osteosynthesis—*bringing ends fracture into close opposition* (Page 1143).

Conformity

If a man does not keep pace with his companions, perhaps it is because he hears a different drummer. Let him keep step to music which he hears, however measured or far away.—Henry David Thoreau



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The Editor's Soliloquy

The Seat Cover

THE MORE COMMITTEE meetings you have, the greater the number of problems to be solved, and the less is accomplished.

As the number of committee members increases, the modifications of the single idea or two become more complex, making a final decision increasingly difficult. Usually this dilemma calls for the appointment of another Investigating Committee and an indefinite delay.

For years and years we have been adequately policing ourselves. Only eternal vigilance and avid study have made it possible for us to practice the high-grade medicine that has become available to all. Through Pathologic Conferences we detect problems that had not been previously solved, and from these we learn. From the burdensome Chart Committees we learn where we might have done better; the Tissue and Procedure Committee evaluates our efficiency in diagnosis and sharpens our wits in solving the multiplicity of variations that can develop from the numerous physiologic and pathologic possibilities almost to the nth power. With the Utilization Committee, the Sterilization Committee and the dozens and dozens of other committees in the State and the County Medical Societies we could occupy ourselves almost on a full-time basis. There are 16 scientific and 29 non-scientific committees in the State Society meeting four times a year or more; 23 committees in the Hennepin County Society convening once or more per year, and 19 committees within the narrower confines of each hospital staff, meeting at frequent intervals.

The Legal Committee usually advises that there might be some legal-technical-socioeconomic problems involved and that the question will therefore have to be handled by our retained counsel. We have become convinced that money is no object where we are protecting our rights.

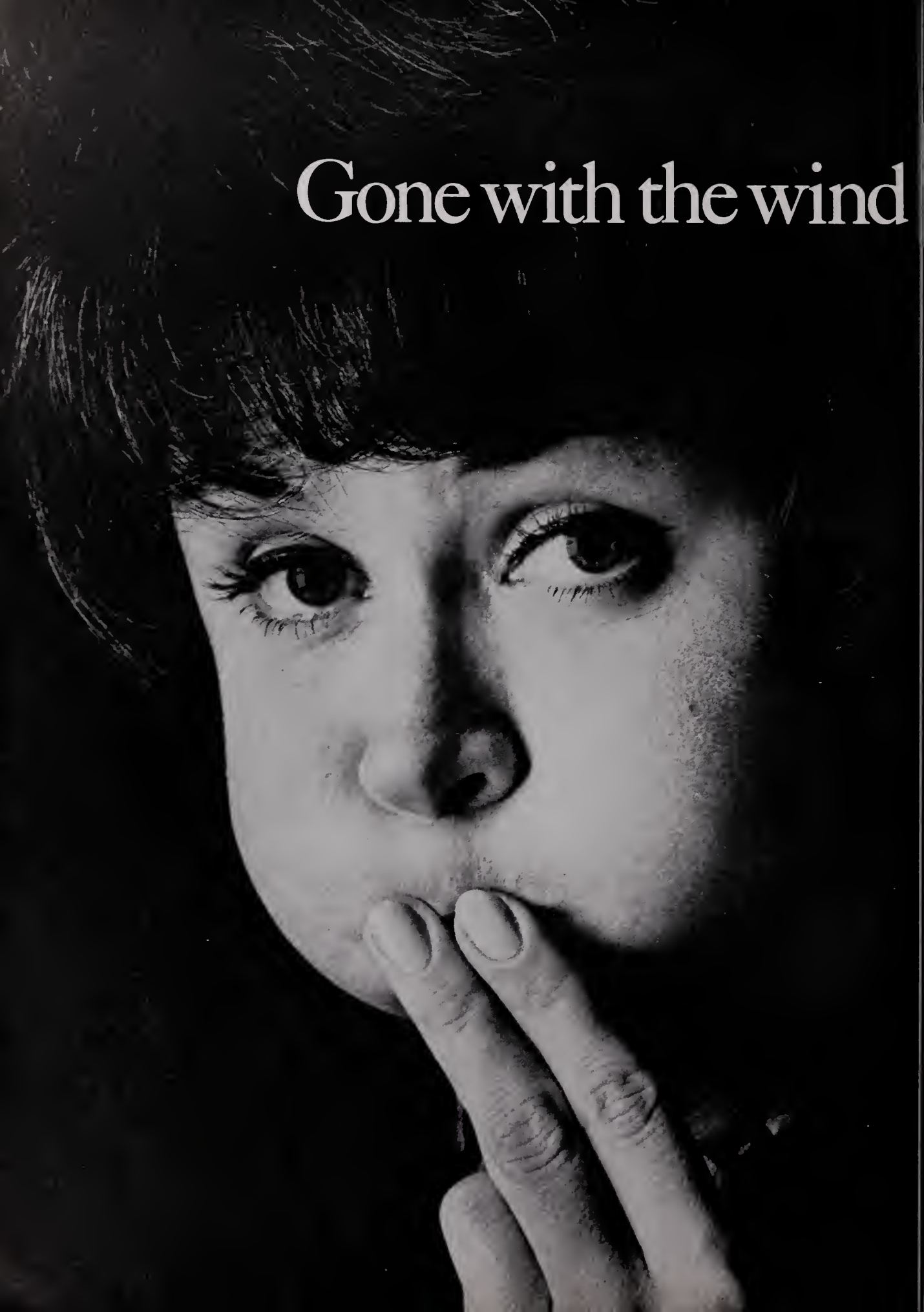
Now must we be cursed with an overall State-financed committee, the Standards-of-Medical-Care Committee with a full time doctor to determine our effective utilization? Has someone scared us into that? Is it really necessary?

The superimposition of another committee to supervise the already existing committees will only so compound the problems and the practice of medicine that soon there will be no time left to attend the patient. "The paralysis of analysis" will set in, as someone has so aptly phrased the procedure of successively instituting a new study to evaluate a previous one which in turn had been instituted to evaluate a still earlier one.

Certainly it is analogous to the purchase of another seat cover to cover the seat cover that covers the seat cover that covers the seat, ad infinitum.

—Carl O. Rice, M.D.

OLD DOC HESS SAYS: During your student days, no matter what your major, you must expect to be subject to the rules and regulations; after graduation, you're on your own.—C.O.R.


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*Slanger, A.: Med. Times *94*:150 (Feb.) 1966.

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Case Report

Thorotrast

Primary Liver Sarcoma 22 Years after the Administration

N. HEGER, M.D.* and S. BAYINDIR, M.D.*

THOROTRAST DAMAGE belongs to the so-called iatrogenic diseases which have become a new field in medicine. It has been shown that modern diagnostic methods can lead to serious damage. This is particularly true in radiological diagnosis with the extensive use of contrast media for the routine demonstration of the lymphatic, venous and arterial systems, as well as in the use of radioactive materials in szintigraphy.

Composition and Properties of Thorotrast

Thorotrast was introduced into radiological diagnosis in 1928/29 because of its excellent shadow density and good general tolerance.[4,9,11] Until 1945 it was used frequently. Thorotrast is a colloidal solution (particle size 3-10mμ) consisting of 25% thorium dioxyde (ThO_2), 25% dextran and 50% water, which decays with a half-life (HL) of 1.39×10^{10} years. The short-lived products of decay are mesothorium (HL = 6.7 years), radiothorium (HL = 1.9 years), and thorium X (HL = 3.64 days). Thorium and its decay products give off primarily highly ionised α-radiation (90% α-radiation, 9% β-radiation and 1% γ-radiation).

Reticulo-histiocyte Accumulation

After radiological examinations such as bronchography, pyelography, salpinography, and fistulography, thorotrast is incompletely eliminated. After intravascular injection (angiography, hepatolienography), however, it is taken up almost completely by the reticulo-histiocyte system.[12] The selective accumulation in the reticulo-histiocyte system and the intensive radiation of the thorotrast-containing tissue must lead to radiation damage. The danger of radiation in patients receiving thorotrast was soon noted.

Blastogenic Potential

Following the production of tumours in experimental animals (Roussy et al.,[14,15] 1934, 1936), the Council of Pharmacy and Chemistry of the American Medical Association and the Swiss Radiological Society forbade the use of thorotrast. Thorotrast was forbidden in France in 1935 and in Russia in 1951. It has not been used in Germany since the studies by K. H. Bauer.[2,3]

The first report of a malignant tumour due to thorotrast administration in man—an angioplastic sarcoma of the liver—was published in 1947.[7]

Case History

The following report of a malignant haemangio-endothelioma in a thorotrast liver can be regarded as characteristic of late thorotrast damage.



Fig. 1—Abdominal radiograph showing deposits of contrast medium (thorotrast) in the liver, spleen and abdominal lymph nodes.

*From the Radiological Section (Head: Dr. med. S. Bayindir) of the Surgical Deparment of the University of Giessen (Director: Prof. K. Vossschulte).

A 55-year-old man had suffered a grenade splinter wound in the right neck region. Formation of a shunt between the communal carotid artery and the internal jugular vein was shown by means of carotid angiography.

Two weeks prior to hospitalisation (22 years after angiography) the patient had suffered brief acute boring pain in the region of the right upper abdomen, radiating into the right shoulder. Thereafter he had had a feeling of pressure in the right upper abdomen.

Examination

On admittance to hospital, a considerable tenderness to pressure in the right upper abdomen was noted and the abdominal wall showed slight resistance. The intestinal loops were distended. There were no pathological peristaltic sounds. Laboratory values, electrocardiogram and radiological examinations excluded the possibility of disease of the gallbladder or biliary tract, pancreatitis, gastrointestinal disease, or a myocardial infarction.

A radiograph of the abdomen (Figure 1) showed contrast-dense deposits in the liver, spleen and abdominal lymph nodes characteristic of thorotrast incorporation. A few hours later, the clinical picture of an acute abdomen and severe shock developed which could not be controlled by conservative treatment. On laparotomy, approximately 2000 ml of liquid blood was found in the abdominal cavity which had come from a rupture, 1.5 cm in diameter in the diaphragmatic surface of the right lobe of the liver. The defect was difficult to repair because of the brittleness of the tissue. Net and spot-like hyalinoses of the capsule and fibrosis of the liver were observed during the operation. Primary liver carcinoma in the area of rupture was suspected. Death due to cardiac failure occurred four hours after operation.

*Catamnesis**

A case is described with severe bleeding from a ruptured haemangio-endothelioma of a thorotrast liver which occurred 22 years after intra-arterial application of thorotrast.

*See Test Your Word Score, page 1131.

Autopsy Findings

The post-mortem findings of the Department of Pathology were as follows:

Thorotrast granuloma 2.5 cm in diameter of the right parapharyngeal space. Large sack-like aneurysm 0.75 cm in diameter of the communal carotid artery without venous connection. Thorotrast liver (Figure 2). Haemangio-endothelioma, 4 cm in diameter of the right lobe of the liver with rupture (Figure 3).

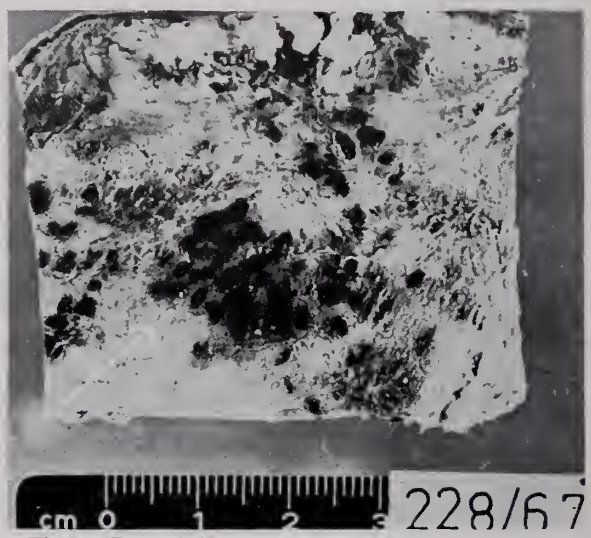


Fig. 3—Part of the cut surface of the liver; haemangio-endothelioma (→); large areas of fibrosis.

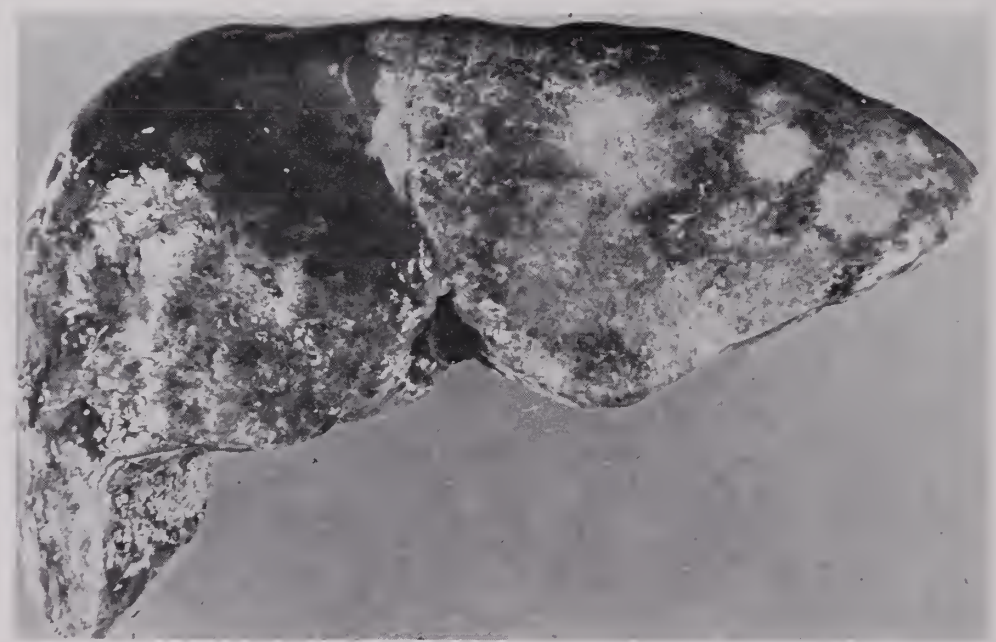


Fig. 2—Thorotrast liver with reticular and spotty fibrosis. Subcapsular bleeding of the right lobe.

Thorotrast spleen. Deposits of thorotrast in the para-aortal and mesenteric lymph nodes, in the bone marrow of the thoracic and lumbar spine and distributed in both adrenals. Marked anaemia of the parenchymatous organs. No equivalents of shock.

Discussion

There is no doubt today that thorotrast is blastogenic due to the continual radiation of tissue by the incorporated thorium and its decay products. Among almost 200 thorotrast tumours in man[1,8,16,18,19] a remarkable number are haemangio-endotheliomas, which are otherwise extremely rare when there has been no injection of thorotrast.[13] The reason for this is not known.

Vascular tumours of the liver due to radiation with massive intraperitoneal bleeding have been described only twice apart from the present report.[6,18]

The total number of malignancies induced by thorotrast is still relatively small. Radiation-induced fibrosis at the site of injection and in the storage organs (liver, spleen, lymph nodes and bone marrow) is the most common form of delayed damage.[17] However, more cases of tumours must be expected because of the intensive α-radiation of the storage organs, the long half-life of thorium and the number of thorotrast carriers which is estimated at 50,000-100,000.[5]

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Sir William Osler

Apart from medicine and his home life, Osler's great loves were old books, children, and practical joking. . . . His appetite for books, rare editions, finely printed, bound, and illustrated steadily increased the more he was able to satisfy it. Here is a characteristic incident. A friend was talking to him of some book when Osler rose from his chair and, unlocking a little cupboard by the fireside, drew out the book in question. "I keep these particular books locked up," he said, "I am so afraid I might steal them myself."*

*Sir Walter Langdon-Brown: Thus We Are Men, 1969.

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(Continued to page 1157)



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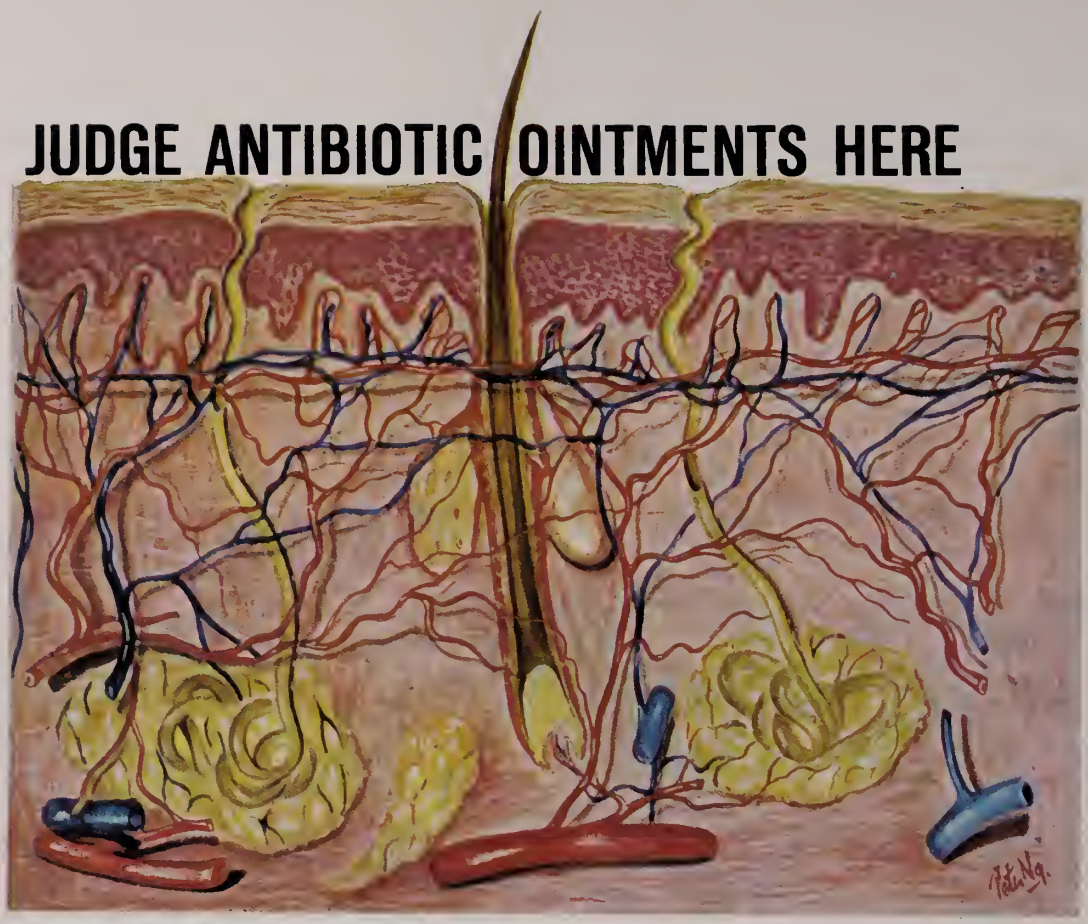
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Clinical Notes

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G. SPITZER, M.D.* and H. ECKE, M.D.*

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Mosaic-like Reposition

Restoration of the distal tibial joint surface by mosaic-like reposition[15] (Table 2) has since been abandoned because of the danger of further devitalisation of the small fragments. In spite of care in technique, the danger of secondary infection in this region is high and leads, even in the best cases, to an ankylosis of the talo-crural joint after prolonged disability and numerous operations. It is better in cases of comminuted fractures to limit the operation to a part of the joint, for example, the medial malleolus, and to carry out an early arthrodesis after consolidation of the remaining fragments. The part of the joint which has undergone osteosynthesis can then be used to advantage as the base for the operation.

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An elegant operative method which is particularly reliable and which allows early weight bearing is our modification of Weber's method of tension band wiring for the treatment of fractures of the medial malleolus. Movement can be allowed immediately after operation and exercise can be started. Full weight bearing is possible after three to six weeks. After nine months there was no significant impairment of working capacity in uncomplicated fractures of the medial malleolus treated by tension band wiring. When considering the operative technique and the osteosynthetic material, it should be noted that *insufficient operative reposition in the region of the malleoli is not only useless but soon results in prolonged and severe disability.* It is advisable therefore to continue with conservative treatment when osteosynthesis cannot be performed under optimal conditions, even when the reposition of the fragments is not satisfactory.

Summary

When comparing the conservative and operative results, it should be noted that only suitable cases, in which perfect reposition was achieved or in which there was no displacement of the fragments, were treated conservatively. All fractures which tended to dislocate or which could not be reduced were operated. The fact that evaluation of working disability after nine to 12 months shows a better numerical value in those treated operatively than in those with closed reduction only, clearly supports the value of correct indication for operation.

The advantages of operative therapy in all malleolar fractures which are difficult to repair or are otherwise complicated are demonstrated on the basis of 271 such fractures treated in the Surgical Department of the University of Giessen between 1960 and 1967.

Immediate osteosynthesis should be carried out in all suitable cases of compound fractures, as the rate of infection of isolated fractures of the malleoli is extremely low. Infection increases, however, if the distal end of the tibia is also involved. In these cases, osteosynthesis should be restricted to a part of the joint which is then used as a base for a later arthrodesis. The rest of the joint should be properly aligned by closed manipulation. Good results can be obtained by screwing, wire pinning, spring screws and other methods of osteosynthesis when it is possible to restore the anatomical conditions. Closed treatment is preferable, however, when osteosynthesis cannot be carried out because of technical difficulties or inadequacy of materials.

*From the Surgical Department of the University of Giessen (Director: Prof. K. Vossschulte).

†See Test Your Word Score, page 1131.

References may be secured from the author.

Interthoracoscapular Amputation in the Treatment of Malignant Tumours of the Upper Extremity

E. WAGNER, M.D.* and H. ECKE, M.D.*

INTERTHORACOSCAPULAR AMPUTATION is the most radical operation in the region of the upper extremity. It has been performed by the authors 15 times in 14 years.

Radical Operation Is Partial Amputation

Survival

The patients in whom the radical operation was not performed had a late mortality rate of 66.6% as compared with 25% in the group which had undergone interthoracoscapular amputation, although the clinical picture was comparable in both groups. The average survival time also shows that the patients who underwent the radical operation have a far higher five-year survival rate than the other group. Ten of the radically operated patients are still under continuous control by the authors and thus improve the statistics. In the group of patients with non-radical amputations, two thirds died within the first two years after operation.

Sequela

In the follow-up study of patients who had undergone interthoracoscapular amputation, a scoliosis, convex towards the amputated side in the region of the thoracic spine, was occasionally observed. However, it caused little discomfort. Increase in blood pressure due to amputation as reported by Leriche was not found in any of the patients, even 10 years or more after operation. A nine-month-old girl with myxosarcoma of the upper arm underwent the radical operation. Her development has been normal and she is now in her sixth year. She shows a tendency to scoliosis, however, and needs compensatory physiotherapy.

Postoperative Mortality

In this study, interthoracoscapular amputation has been found to be far the best therapy for osteogenic sarcoma of the upper extremity. The operation was well tolerated and there were no operative deaths. One quarter of the patients died during the postoperative treatment as compared to two thirds of those who underwent partial amputation. An endoprosthesis was implanted in the upper arm in two cases with giant cell tumours Types I and II (Jaffe-Lichtenstein), which are rightly regarded by Hellner as malignant. In one case, pulmonary metastases were found five months later, although the pathology had shown no definite malignancy. The patient is still alive, but a radical operation might have saved his life in the long run. The better results seen after radical amputation as compared to partial operation may be due to the fact that in interthoracoscapular amputation the operation is performed at a considerable distance from the tumour and contact with neoplastic tissue is thus avoided.

Summary

Fifteen of 64 patients with malignancies of the upper extremity who were treated by radical operation had a better five-year survival rate and lower total mortality than the corresponding group which had a partial amputation. For this reason the arguments against the radical operation should not be over-emphasised and indication for interthoracoscapular amputation should be extended.

*From the Surgical Department of the University of Giessen (Director: Prof. K. Vossschulte).

The actions of the official Tincture and Extract of Belladonna result chiefly from their Atropine content . . . conclude Goodman and Gilman

THE PHARMACOLOGICAL BASIS OF THERAPEUTICS
3rd Edition, page 522



ANTROCOL®

Antrocol provides the prompt, predictable antisecretory action of the belladonna alkaloid, atropine, fortified with sedation and blended with Bensulfoid, contributing to even absorption.



Each tablet or capsule contains: Atropine sulfate, 0.324 mg.; Phenobarbital, 16 mg. (may be habit forming); Bensulfoid, 65 mg. (see white section PDR). The atropine content of Antrocol is the maximum amount the average patient can take at six hour intervals over long periods with comfort.

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Caution: Federal law prohibits dispensing without prescription.

PRESCRIBING INFORMATION

Contraindicated in glaucoma. Use cautiously in prostatic hypertrophy. Side-effects of toxic dose of atropine: flushing, dryness of mouth, cycloplegia, tachycardia and urinary retention.

DOSAGE: One tablet or capsule after each meal to correct emotional stress and normalize gastric secretions. In treating peptic ulcer, doses at regular intervals up to eight (8) tablets or capsules per day to provide the proper gastric titer for healing. After ulcer has healed, one tablet or capsule after each meal to maintain a titer unfavorable to recurrence.

Clinical supply available to physicians.

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Roche announces

Efudex®

(fluorouracil) cream/solution

for the treatment of solar/actinic keratoses... a topical alternative to conventional therapy

1/22/68—Treatment with 5% 5-FU cream commences. Patient K.L. showing widespread but mild solar keratoses (also known as actinic keratoses).



Fluorouracil—the Roche contribution

In 1962, Roche Laboratories introduced Fluorouracil Roche® (5-fluorouracil). Early clinical work with this drug suggested that it possessed a selective cytotoxic activity when applied topically to certain kinds of lesions. Based on this work and years of clinical trials, a standardized form of topical fluorouracil can now be recommended for treatment of multiple solar or actinic keratoses.

Efudex®(fluorouracil)—a new alternative to conventional therapy

Efudex presents the physician with a topical alternative to surgery in the treatment of solar or actinic keratoses. It is effective, comparatively inexpensive and especially well-suited for treatment of multiple lesions. Important, too, is the highly desirable cosmetic result. Clinical experience demonstrates that treatment with Efudex results in an extremely low incidence of scarring.*

Highly effective on first and later applications

In clinical trials, depending on the dosage form and strength used, complete involution occurred in 77 to 88 per cent of lesions following treatment. The rate of recurrence was low, ranging from 1.7 to 5.6 per cent up to a year after completion of therapy. When lesions did recur or new ones appeared, repeated courses of Efudex therapy proved effective.*

2/2/68—After 11 days of treatment. Erythema is seen at site of keratoses. In addition, numerous lesions not apparent prior to therapy have become manifest by sharply defined reactions. Intervening skin, also treated, shows no response to therapy.

2/19/69—One year after cessation of therapy. Skin appears clear with no evidence of scarring. Examination reveals lack of recurrence or the formation of new lesions.



Predictable sequence of therapeutic response

Two to four weeks constitutes a typical course of Efudex therapy. The response is usually characteristic and predictable. After three or four days of treatment, erythema begins to appear in the area of the keratoses. This is followed by an intense inflammatory response, scaling and occasionally moderate tenderness or pain. The height of the inflammatory reaction generally occurs two weeks after the start of therapy, and then begins to subside as treatment is stopped. Within two weeks of discontinuing medication, the inflammation is usually gone. A mild erythema may remain for two to three months before gradually receding.

Selective—with a high degree of safety

Despite the temporary unsightliness and discomfort of the inflammatory episode, Efudex is, in general, more readily tolerated than surgery. Clinical work shows the intense inflammatory response to be limited to the area of the lesion. Normal skin is not similarly affected. Another measure of Efudex safety: systemic absorption of topical fluorouracil was insignificant, indicating a low risk of systemic toxicity.*

Two strengths—two convenient dosage forms

Efudex is available as a 2% or 5% solution or as a 5% cream. It is applied twice daily by the patient with a nonmetal applicator or suitable glove.

Before prescribing Efudex, however, there are two important considerations. First, please consult the complete prescribing information for precautions, warnings and adverse reactions. Second, advise the patient that treated lesions should respond with the characteristic but transient inflammation. A positive sign that Efudex is working for them.

*Data on file, Hoffmann-La Roche Inc., Nutley, New Jersey.

2% and 5% Solutions; 5% Cream Applied twice daily—resolves solar or actinic keratoses.

new Efudex® (fluorouracil) cream/solution



For full prescribing information, please see the following page.

Roche introduces

Efudex®

(fluorouracil) cream/solution the new standardized topical for solar/actinic keratoses

Description: Efudex solutions and cream are topical preparations containing the fluorinated pyrimidine 5-fluorouracil, an antineoplastic antimetabolite.

Efudex Solution consists of 2% or 5% fluorouracil on a weight/weight basis, compounded with propylene glycol, tris-(hydroxymethyl) aminomethane, hydroxypropyl cellulose, parabens (methyl and propyl) and disodium edetate.

Efudex Cream contains 5% fluorouracil in a vanishing cream base consisting of white petrolatum, stearyl alcohol, propylene glycol, polysorbate 60 and parabens (methyl and propyl).

Actions: There is evidence that the metabolism of fluorouracil in the anabolic pathway blocks the methylation reaction of deoxyuridylic acid to thymidylic acid. In this fashion fluorouracil interferes with the synthesis of deoxyribonucleic acid (DNA) and to a lesser extent inhibits the formation of ribonucleic acid (RNA). Since DNA and RNA are essential for cell division and growth, the effect of fluorouracil may be to create a thymine deficiency which provokes unbalanced growth and death of the cell. The effects of DNA and RNA deprivation are most marked on those cells which grow more rapidly and which take up fluorouracil at a more rapid pace. The catabolic metabolism of fluorouracil results in degradative products (*e.g.*, CO_2, urea, α-fluoro-β-alanine) which are inactive.

Studies in man with topical application of ^{14}C-labeled Efudex demonstrated insignificant absorption as measured by ^{14}C content of plasma, urine and respiratory CO_2.

Indications: Efudex is recommended for the topical treatment of multiple actinic or solar keratoses.

Contraindications: Efudex is contraindicated in patients with known hypersensitivity to any of its components.

Warnings: If an occlusive dressing is used, there may be an increase in the incidence of inflammatory reactions in the adjacent normal skin.

Prolonged exposure to ultraviolet rays should be avoided while under treatment with Efudex because the intensity of the reaction may be increased.

Usage in Pregnancy: Safety for use in pregnancy has not been established.

Precautions: If Efudex is applied with the fingers, the hands should be washed immediately afterward. Efudex should be applied with care near the eyes, nose and mouth. To rule out the presence of a frank neoplasm, a biopsy should be made of those areas failing to respond to treatment or recurring after treatment.

Adverse Reactions: The most frequently encountered local reactions were pain, pruritus, hyperpigmentation and burning at the site of application. Other local reactions included dermatitis, scarring, soreness and tenderness.

Also reported were insomnia, stomatitis, suppuration, scaling, swelling, irritability, medicinal taste, photosensitivity and lacrimation.

Laboratory abnormalities reported were leukocytosis, thrombocytopenia, toxic granulation and eosinophilia.

Dosage and Administration: Efudex should be applied twice daily with a nonmetal applicator or suitable glove in an amount of the solution or cream sufficient to cover the lesion. When Efudex is applied to a lesion, a response occurs with the following sequence: erythema, usually followed by vesiculation, erosion, ulceration, necrosis and epithelization. The lower frequency and intensity of activity in adjacent normal skin indicate a selective cytotoxic property. Medication should be continued until the inflammatory reaction reaches the erosion, necrosis and ulceration stage, at which time use of the drug should be terminated. The usual duration of therapy is from 2 to 4 weeks. Complete healing of the lesion may not be evident for 1 to 2 months following cessation of Efudex therapy.

How Supplied: Efudex Solution, 10-ml drop dispensers—containing 2% or 5% fluorouracil on a weight/weight basis, compounded with propylene glycol, tris(hydroxymethyl)aminomethane, hydroxypropyl cellulose, parabens (methyl and propyl) and disodium edetate.

Efudex Cream, 25-Gm tubes—containing 5% fluorouracil in a vanishing cream base consisting of white petrolatum, stearyl alcohol, propylene glycol, polysorbate 60 and parabens (methyl and propyl).

Clinical Studies: The effectiveness of the three preparations as determined by complete involution of solar keratoses was: 2% Solution, 77% of 282 lesions; 5% Solution, 88% of 202 lesions; and 5% Cream, 85% of 189 lesions. In those lesions where complete involution followed treatment, the rate of possible recurrences observed clinically at periods up to 12 months or more was: 2% Solution, 4.6% of 218 lesions; 5% Solution, 1.7% of 177 lesions; and 5% Cream, 5.6% of 160 lesions. Because of the toxic potential of fluorouracil, some physicians preferred to use the 2% solution when large areas were to be treated. Approximately 30% of the lesions required treatment for two weeks or less; approximately 78% required four weeks or less for adequate treatment.

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Special Article

Giessen University

Historical and Current Aspects

PROFESSOR KARL VOSSSCHULTE, M.D.*

Giessen is situated near Frankfurt-on-the-Main and today has a population of approximately 75,000. Since the end of the war, trade and industry have contributed to its vitality and prosperous development.

Ludoviciana

The university was founded in 1607 by Ludwig (Ludovic) V. Landgrave of Hessen and therefore named "Ludwigs-University" or "Ludoviciana" in academic language. The basis of its educational curriculum was formed by the four classic faculties: Theology, Philosophy, Jurisprudence and Medicine.

In the ups and downs of its history "Ludwigs-University" experienced many difficult periods. It had, however, enough vitality to overcome all its misfortunes arising from the political situation, which threatened its development. In the fields of medicine and the natural sciences it gained worldwide renown in the 19th century. *Wilhelm Conrad Roentgen,* discoverer of the "Roentgen-rays" (x-rays), was a member of the Ludoviciana's teaching staff for nearly 10 years. *Justus von Liebig* did his most important scientific work in Giessen. His most famous book "Die organische Chemie in ihrer Anwendung auf Agrikultur und Physiologie" (Organic Chemistry in its Application to Agriculture and Physiology) also dates from that time (1840).

Aftermath of World War II

The last war and its aftermath had hit town and university so hard that the situation seemed hopeless. Part of the university's clinics and institutes were completely destroyed; another part was unfit for scientific and practical work. The extent of destruction caused a desperate decision: the Ludoviciana was the only German university to be closed in 1945, thus extinguishing its name. However, the potential of the institution, developed from centuries of tradition, was not moribund. It created new life from out of the ashes. As early as 1946 great skill and an undogmatic strategy, adapted to the confusion of the postwar period, led to the resumption of college work within a modest frame and without university privilege. After painstaking and often disappointing efforts a new form emerged from these beginnings. From the outset and in its further development this form was decisively influenced by three factors. 1. Financial means were extremely limited. 2. The university as the realization of a "universitas literarum" was to be replaced by an institute concentrating in more specialized fields. 3. Commensurate with the economic

*From the Department of Surgery, Director; University of Giessen.

possibilities and following the example of American universities, only a limited number of students was to be admitted.

Justus-Liebig-University

Fortunately two faculties—agriculture and veterinary medicine—were functioning again in 1946 to such an extent that relatively acceptable teaching could be resumed. Supplemented by several professorships for the natural sciences, the meagre frame for a "College of Natural Science and Biology" was provided. The branch of human medicine was affiliated with it in the form of an academy with clinical instruction courses for students. Scantily equipped, but with great courage, this new institute entered the next decade, approaching 1957 and the 350th anniversary of the Giessen University. This anniversary could not be overlooked by the political and cultural consciousness of the Land Hessen. As the economic situation had improved in the meantime, the anniversary gave occasion for completing the college and restoring its university status under the name "Justus-Liebig-University." With this act the heritage of the Ludoviciana was saved, and development thereafter took a more gratifying course. Today Giessen University embraces six faculties: Philosophy, Jurisprudence and Economics, Natural Science, Medicine, Veterinary Medicine, and Agriculture. In addition it has a Department of Pedagogics.

The institutes and clinics of the medical faculty are situated on a single campus and provide full training facilities for about 650 students. No substantial increase in this number is intended for the future.

Bedside Teaching

With this conception Giessen is the first German medical faculty to have taken steps towards a reform of the study of medicine. It has also adopted methods of the American teaching system which is accentuated by bedside-teaching in small groups.

Clinical Lecture

In this respect the traditional German course of studies doubtless had some shortcomings, because the semesters of clinical work consisted mainly of lectures. However, it would be a mistake to believe that this teaching was purely theoretical; nothing could be farther from the truth. In the clinical lecture, pathological anatomy, pathophysiology, etiology, epidemiology, etc. have always been discussed and illustrated with specific examples. The candidate had to acquire the fundamentals before being asked to apply them. This application he learned by working in institutes and clinics for two years. Only then could he become a certified physician. Whether this traditional German method has achieved less than the new one promises, remains to be seen. So far I have been unable to discern a marked difference. But I am more and more assailed by doubts as to whether bedside-teaching can replace the value of the clinical lecture.

Adequate Examination

In the last analysis both methods are didactically useful, provided efficiency is constantly controlled by an adequate examination system, which, so far, has received too little attention in Germany and will have to be stressed in the

future curriculum. No student likes to hear this, but already the examinee, when finishing his studies, will be able to recognize and utilize its value; and if he should become the father of a medical student, nothing will probably seem more reasonable to him than a course of studies regulated step by step through adequate efficiency tests.

The New Didactics

Medicine is a special branch of the natural sciences which serves the civilizing progress of mankind. The universities are called upon to show the way to this goal and to apply the most efficient teaching methods, which means abandoning traditional and convenient practices for the sake of new didactic knowledge. This development is now taking place in Germany. In the medical field it is implemented by the fact that the clinical lecture keeps its place in the curriculum and is supplemented by bedside-teaching in groups.

Relating To My Life

I was much troubled with the tumor in my neck, as the physician and surgeon wished first to disperse this excrescence, afterwards, as they said, to draw it to a head, and at last thought it best to open it; so for a long time I had to suffer more from inconvenience than pain, although towards the end of the cure the continual touching with lunar caustic and other corrosive substances could not but give me very disagreeable prospects for every fresh day. The physician and surgeon both belonged to the Pious Separatists, although both were of highly different natural characters. The surgeon, a slender, well-built man, of easy and skilful hand, was unfortunately somewhat hectic, but endured his condition with truly Christian patience, and did not suffer his disease to perplex him in his profession.

The physician was an inexplicable, sly-looking, fair-spoken, and, besides, an abstruse, man. Being active and attentive, he was consoling to the sick; but, more than by all this, he extended his practice by the gift of showing in the background some mysterious medicines prepared by himself, of which no one could speak, since with us the physicians were strictly prohibited from making up their own prescriptions. With certain powders, which may have been some kind of digestive, he was not so reserved, but that powerful salt, which could only be applied in the greatest danger, was only mentioned among believers; although no one had yet seen it or traced its effects.

In the meantime, a very severe trial was preparing for me: for a disturbed, and, one might even say, for certain moments, destroyed digestion, excited such symptoms, that, in great tribulation, I thought I should lose my life; and none of the remedies applied would produce any further effect. In this last extremity my distressed mother constrained the embarrassed physician with the greatest vehemence to come out with his universal medicine. After a long refusal, he hastened home at the dead of night, and returned with a little glass of crystallized dry salt, which was dissolved in water, and swallowed by the patient. It had a decidedly alkaline taste. The salt was scarcely taken than my situation appeared relieved; and from that moment the disease took a turn which, by degrees, led to my recovery.*

*Johann Wolfgang Goethe: Autobiography.

Menrium® treats the menopausal symptoms that bother him most.



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His wife has a lot of different menopausal symptoms, but only a few really irritate *him*. Her hot flashes, her vertigo, her palpitations—that's *her* problem. What really bothers him is her nervousness, her irritability and her excessive anxiety, often expressed by endless "book-shuffling, chain-smoking, reading-lamp" insomnia!

Menrium takes care of hot flashes, vertigo, palpitations in most menopausal women. Menrium provides the well-known antianxiety action of chlordiazepoxide (Librium®) and water-soluble esterified estrogens. It therefore relieves more symptoms than either component separately. It takes care of the vasomotor symptoms as well as the emotional symptoms. This means the symptoms that bother his wife most. And the symptoms that irritate him most.

So, to help them both get through her menopause, remember Menrium.



Before prescribing, please consult complete product information, a summary of which follows:

Indications: Management of manifestations generally associated with the menopausal syndrome—anxiety and tension, vasomotor complaints and hormonal deficiency states.

Contraindications: Women with cancer of breast or genitalia, except inoperable cases, and those with known hypersensitivity to chlordiazepoxide and/or esterified estrogens.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Exclude other possible causes of menopausal syndrome manifestations, such as pregnancy. Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions) similar to those seen with barbiturates have been reported following discontinuance of chlordiazepoxide HCl. Potential benefits of use in pregnancy, lactation or women of childbearing age should be weighed against possible hazards to mother and child. Clinical data inadequate on safety in pregnancy.

Precautions: In elderly and debilitated patients, limit dosage to smallest effective amount of chlordiazepoxide (initially 10 mg or less per day) to preclude ataxia or oversedation; increase gradually as needed and tolerated. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects—particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in patients with impaired renal or hepatic function. Paradoxical reactions to chlordiazepoxide (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients. Employ usual precautions in the treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation very rarely reported in patients receiving Librium® (chlordiazepoxide) and oral anticoagulants.

Adverse Reactions: Untoward effects seen with either compound alone may occur with Menrium. With chlordiazepoxide, drowsiness, ataxia and confusion reported in some patients, particularly in the elderly and debilitated; while usually avoided by proper dosage adjustment, these are occasionally observed at lower dosage ranges. Also reported have been a few instances of syncope; isolated occurrences of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido, and occasional reports of blood dyscrasias, including agranulocytosis, jaundice and hepatic dysfunction. Periodic blood counts and liver function tests advisable during protracted treatment. Changes in EEG patterns (low-voltage fast activity) observed during and after chlordiazepoxide treatment.

With estrogens, headache, nausea and vomiting, anorexia, gastrointestinal discomfort, dysuria and urinary frequency, jitteriness, breast engorgement, formation of breast cysts, skin rashes and pruritus occasionally seen. Administration may also be associated with uterine bleeding and/or followed by withdrawal bleeding.

Usual Dosage: One tablet t.i.d. for 21 days, followed by one-week rest periods.

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5 mg chlordiazepoxide	5-2	0.2 mg water-soluble esterified estrogens
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BREAKUP—symbol of the impact of emotional stress. But when the stress exceeds transient rage or depression—and settles into a chronic mixed anxiety depression state—combined tranquilizer-antidepressant therapy could be indicated.





FOR MODERATE TO SEVERE ANXIETY WITH COEXISTING DEPRESSION

TRIAVIL®

TRANQUILIZER-ANTIDEPRESSANT

Containing perphenazine and amitriptyline HCl

For prescribing information, including indications, contraindications, warnings, precautions, and side effects, please see following page.

FOR MODERATE TO SEVERE ANXIETY WITH COEXISTING DEPRESSION

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TRANQUILIZER-ANTIDEPRESSANT

Containing perphenazine and amitriptyline HCl

TRIAVIL®2-10: Each tablet contains 2 mg. of perphenazine and 10 mg. of amitriptyline hydrochloride.

TRIAVIL®2-25: Each tablet contains 2 mg. of perphenazine and 25 mg. of amitriptyline hydrochloride.

TRIAVIL®4-10: Each tablet contains 4 mg. of perphenazine and 10 mg. of amitriptyline hydrochloride.

TRIAVIL®4-25: Each tablet contains 4 mg. of perphenazine and 25 mg. of amitriptyline hydrochloride.

INDICATIONS: Patients with moderate to severe anxiety and/or agitation and depressed mood; patients with depression in whom anxiety and/or agitation are severe; patients with depression and anxiety in association with chronic physical disease; schizophrenics with associated depressive symptoms.

CONTRAINDICATIONS: Central nervous system depression from drugs (barbiturates, alcohol, narcotics, analgesics, antihistamines); bone marrow depression; pregnancy; and in patients with known hypersensitivity to phenothiazines or amitriptyline. Do not give in combination with MAOI drugs because of possible potentiation that may even cause death. Allow at least two weeks between therapies. In such patients therapy with TRIAVIL should be initiated cautiously, with gradual increase in the dosage required to obtain a satisfactory response. Do not give concomitantly with guanethidine or similarly acting compounds since it may block the antihypertensive effect.

WARNINGS: Patients should be warned against driving a car or operating machinery or apparatus requiring alert attention, and that response to alcohol may be increased.

PRECAUTIONS: Suicide is always a possibility in mental depression and may remain until significant remission occurs. Supervise patients closely in case they may require hospitalization or concomitant electroshock therapy. Untoward reactions have been reported after the combined use of antidepressant agents having various modes of activity. Accordingly, consider possibility of potentiation in combined use of antidepressants. Use with caution in patients with glaucoma and those with problems of urinary retention. Perphenazine can lower the convulsive threshold in susceptible individuals. It should be given with caution to patients with convulsive disorders. Dosage of the anticonvulsive agent may have to be increased. Not recommended for use in children. Mania or hypomania may be precipitated in manic-depressives (perphenazine in TRIAVIL seems to reduce likelihood of this effect). If hypotension develops, epinephrine should not be employed, as its action is blocked and partially reversed by perphenazine. Caution patients about errors of judgment due to change in mood.

ADVERSE REACTIONS: Similar to those reported with either constituent alone.

Perphenazine: Should not be used indiscriminately. Use caution in patients who have previously exhibited severe reactions to other phenothiazines. Likelihood of untoward actions greater with high doses. Closely supervise with any dosage. Side effects may be any of those reported with phenothiazine drugs: extrapyramidal symptoms (opisthotonos, oculogyric crisis, hyperreflexia, dystonia, akathisia, dyskinesia, parkinsonism) usually controlled by the concomitant use of effective antiparkinsonian drugs and/or by reduction in dosage, but sometimes persist after discontinuation of the phenothiazine; skin disorders (photosensitivity, itching, erythema, urticaria, eczema, up to exfoliative dermatitis); other allergic reactions (asthma, laryngeal edema, angioneurotic edema, anaphylactoid reactions); peripheral edema; reversed epinephrine effect; hyperglycemia; endocrine disturbances (lactation, galactorrhea, disturbances of menstrual cycle); altered cerebrospinal fluid proteins; paradoxical excitement; EKG abnormalities (quinidine-like effect); reactivation of psychotic processes; catatonic-like states; autonomic reactions, such as dryness of the mouth, headache, nausea, vomiting, constipation, obstipation, urinary frequency, blurred vision, nasal congestion, and a change in the pulse rate; hypnotic effects; pigmentary retinopathy; corneal and lenticular pigmentation; occasional lassitude; muscle weakness; mild insomnia. Other adverse reactions reported with various phenothiazine compounds, but not with perphenazine, include blood dyscrasias (pancytopenia, thrombocytopenic purpura, leukopenia, agranulocytosis, eosinophilia); liver damage (jaundice, biliary stasis); grand mal convulsions; cerebral edema; polyphagia; photophobia; skin pigmentation; and failure of ejaculation. Significant unexplained rise in body temperature may suggest intolerance to perphenazine, in which case discontinue. Antiemetic effect may obscure signs of toxicity due to overdosage of other drugs or make diagnosis of other disorders such as brain tumors or intestinal obstruction difficult. May potentiate the action of central nervous system depressants (opiates, analgesics, antihistamines, barbiturates, alcohol) and atropine. In concurrent therapy with any of these, TRIAVIL should be given in reduced dosage. May also potentiate the action of heat and phosphorous insecticides.

Amitriptyline: Careful observation of all patients recommended. Side effects include drowsiness (may occur within the first few days of therapy); dizziness; nausea; excitement; hypertension; fainting; fine tremor; jitteriness; weakness; headache; heartburn; anorexia; increased perspiration; incoordination; impotence; increased appetite and weight gain; allergic-type reactions manifested by skin rash, swelling of face and tongue, itching; numbness and tingling of limbs, including peripheral neuropathy; activation of latent schizophrenia (however, the perphenazine content may prevent this reaction in some cases); epileptiform seizures; temporary confusion, disturbed concentration, or transient visual hallucinations on high doses; evidence of anticholinergic activity, such as tachycardia, dryness of mouth, stomatitis, blurring of vision, reversible dilatation of the urinary tract, urinary retention, constipation, paralytic ileus; agranulocytosis; jaundice. Elderly patients and adolescents can often be managed on lower dosage levels.

For more detailed information, consult your MSD Representative or see the package circular. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486.

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Classified Advertisements

(Continued from page 1140)

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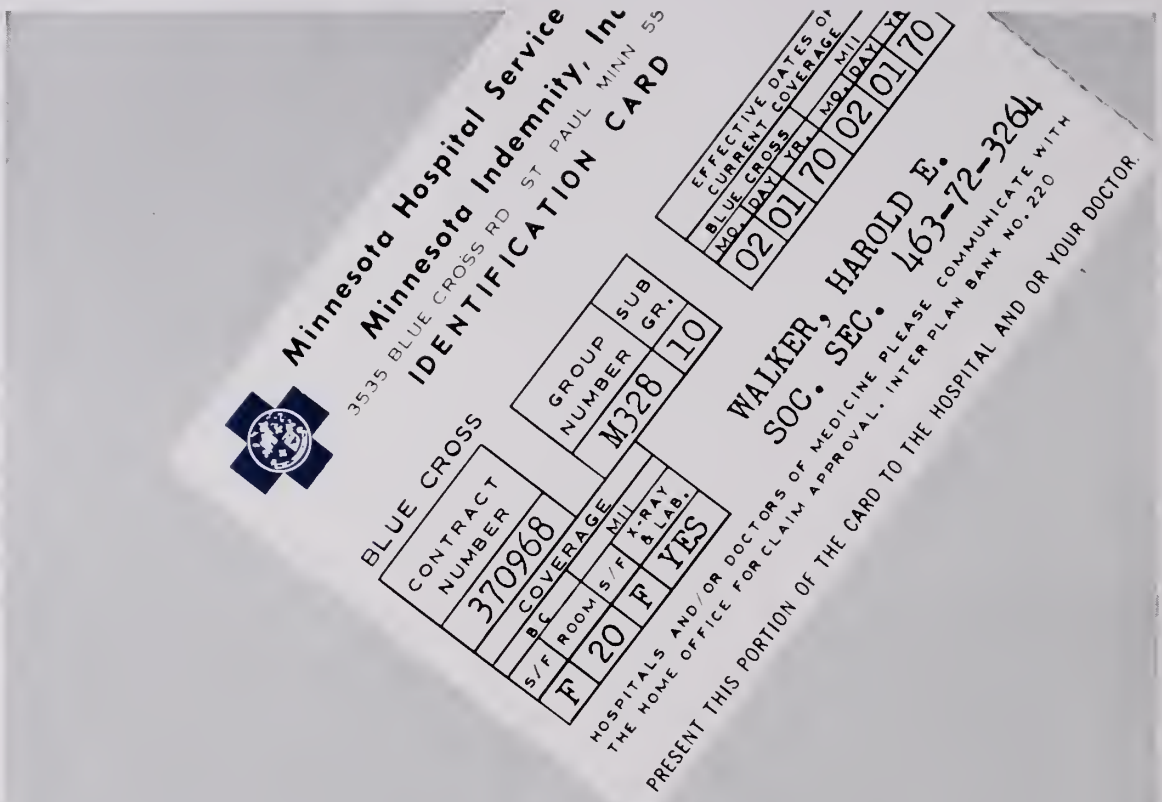
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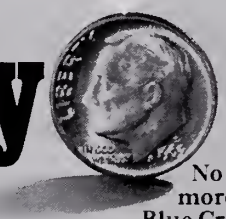
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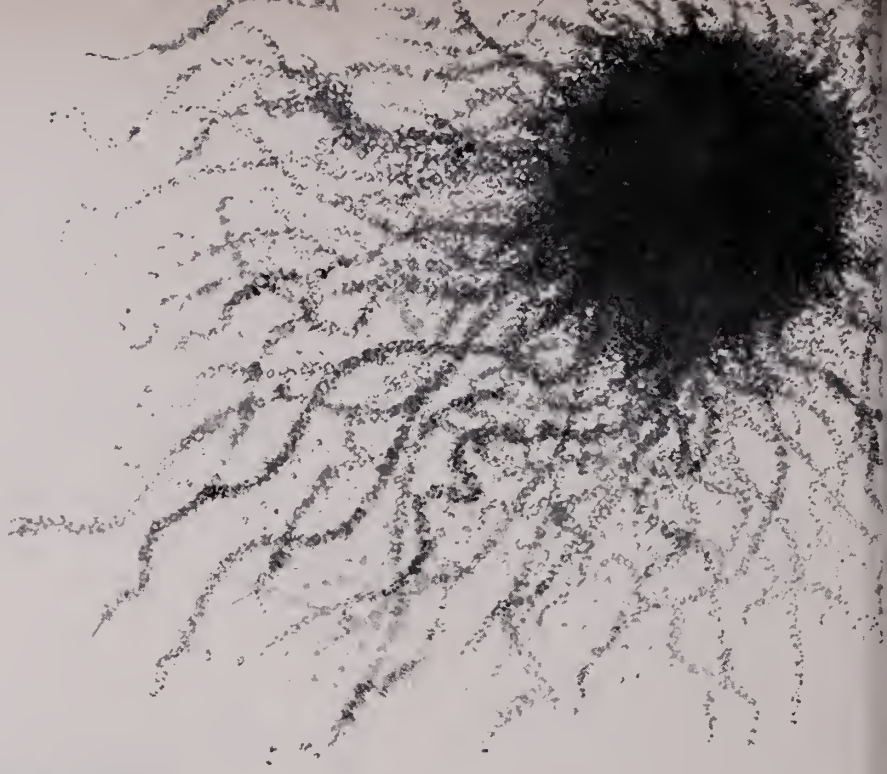
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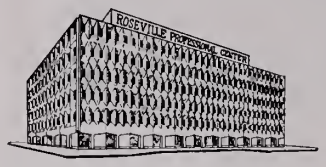
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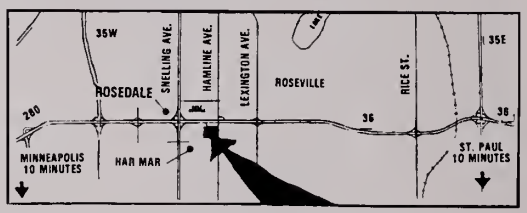
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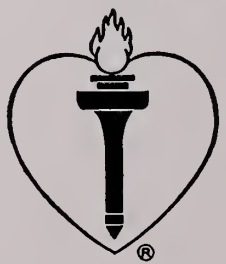
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President's Letter

Minnesota Physicians and Our State Board of Health

PART II

ADDITIONAL EVIDENCE of the cooperative relationship between the Minnesota State Board of Health and the medical profession is constituted by the activities and interest in recent years of the Minnesota State Medical Association's Committee on Medical Service (Martin Van Herik, M.D., chairman). This Committee, by means of its Subcommittee on Standards of Medical Care (John L. Falls, M.D., chairman), has investigated the feasibility of evaluating the quality of medical care in hospitals and nursing homes. This study is being conducted in Minnesota to determine whether or not it would be practicable and useful to establish an information col'ection and reporting system and a data bank resource from which evaluations could be made *by physicians* of the quality of medical care being provided in Minnesota hospitals and nursing homes. This mechanism represents the significant contribution of implementing review and analysis of levels of medical care by physicians (peer review) rather than by third-party investigators who would be other than physicians. The importance of this kind of review to the medical community at large cannot be overemphasized.

The Minnesota State Board of Health has worked closely with the Minnesota State Medical Association in helping to make this study a reality, as have other organizations, including the Northlands Regional Medical Program, Inc., Blue Shield of Minnesota, the Minnesota Hospital Association, Inc., and the Minnesota Blue Cross.

I should like to comment on one more example of the good working relationship between the State Board of Health and the medical profession in Minnesota. Very likely there has not been a more significant federal program affecting the American medical and health-care system in recent years than the Medicare program, which also affects some 20 million people older than 65 years in the United States. The State Board of Health was named as the agency to administer the Medicare program in Minnesota.

The relative degree of success achieved by this program could not have been reached without the sincere efforts and admirable cooperation of Minnesota physicians with the State Board of Health. Minnesota physicians have spent countless thousands of hours in this endeavor in assisting hospitals, extended-care facilities, and home-health agencies to meet the Federal requirements, explaining benefit coverages and administrative detail to their patients both in office practice and in health-care institutions, and in serving on utilization review committees throughout the State. In addition to regular service on such committees, more than 200 physicians spent in excess of five hours each at State Board of Health workshops on utilization review during the fall of 1968. Without the dedicated and persevering cooperation of physicians throughout the State, no governmental agency could have implemented a program of this magnitude.

How fortunate we Minnesota physicians are to have such dedicated executive secretaries as Mr. Harold W. Brunn, of the Minnesota State Medical Association, and Dr. Robert N. Barr of the Minnesota State Board of Health, to assist us in delivering health care to the people of Minnesota!

R. J. Jackman

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A DECADE HAS passed since our group presented observations on patients with bacteremia due to *Bacteroides*.[1] Recent laboratory and clinical experiences with such cases stimulated our interest in further reviewing this type of infection.

Methods and Materials

Group Studied

The histories of all patients with blood cultures positive for *Bacteroides* during the period from March 1, 1959, through June 30, 1969, were reviewed. Criteria for inclusion in this study were: one or more premortem blood cultures positive for *Bacteroides* and satisfactory clinical information to corroborate the presence of bacteremia. In the time period noted, a total of 296 blood cultures positive for *Bacteroides* were isolated from 134 patients. Eleven patients were excluded from this study on the basis of inadequate clinical information. A final total of 123 patients with 285 positive blood cultures were accepted as authentic examples of bacteremia and constitute the basis for this report; in no instance was *Bacteroides* considered a contaminant.

Blood Cultures

During most of the time period covered by this study, samples of the patients' blood were inoculated into dextrose brain broth (6 to 8 ml/35 ml of media) and into several pour plates. The broths were examined periodically during a three-week incubation period. During the last year of the study, samples of the patients' blood (5 ml/50 ml of media in the latter half of 1968 and 10 ml/100 ml of media beginning in 1969) were inoculated instead into both tryptic soy broth (Difco) under vacuum and 10% CO_2 and thiol broth (Difco) under vacuum and 10% CO_2. These were examined daily during a minimal incubation period of two weeks. Routine subcultures were made at 48 hours to chocolate blood agar with yeast extract enrichment (GC Agar, BBL), which was incubated at 37 C in 10% CO_2 for 48 hours.

Identification of Bacteroidaceae

Bacteroides were identified by their ability to grow under anaerobic conditions (Brewer jar) but not aerobically or under increased CO_2 tension. The criteria for identification included isolation of obligately anaerobic, nonsporeforming, gram-negative, pleomorphic or nonpleomorphic bacilli. The isolates were not speciated until 1968.

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TABLE 1
Classification of Bacteroidaceae

Organism	Growth in 10% bile	Esculin hydrolysis	pH in glucose	Penicillin sensitivity	pro-H_2S duction	pro-Indole duction	Gelatin liquefaction
*Bacteroides fragilis**	Yes	Yes	<5.4	Resistant	No	Yes or no	No
*B. oralis**	No	Yes	<5.4	Sensitive	No	Yes or no	No
B. funduliformis†	Yes or no	No	>5.6	Sensitive	Yes	Yes (++)	No
B. melaninogenicus‡	No	No	>5.6	Sensitive	Yes	Yes (+)	No
Bacteroides spp.*	No	No	>5.6	Sensitive	No	Yes or no	No
Fusobacterium spp.§	No	No	>6.0	Sensitive	Yes	Yes or no	No

*Nonpleomorphic.
†Swellings, round bodies with vacuoles.
‡Small, coccoid (black colonies on lysed blood after 4 days).
§Straight or bent, slender, with tapered ends (in sheaves, may have gram-positive granules).

In 1968, speciation of the obligately anaerobic, gram-negative bacilli was carried out according to the criteria of Rosebury,[2] Sonnenwirth and associates,[3] Smith and Holdeman,[4] and Dowell and Hawkins.[5] The Gas-Pak (BBL) system was used to achieve anaerobiosis. Table 1 provides a summary of the criteria used.

Antibiotic Susceptibility Tests

Prior to 1968, antibiotic susceptibility tests giving minimal inhibitory concentration (MIC) were performed by the tube-dilution procedure using 8-ml volumes of fluid thioglycollate. One milliliter of the appropriate concentration of antibiotic and 1 ml of a slightly turbid suspension of the organism in thioglycollate were added to each tube and the tubes examined for turbidity after 48 hours of incubation. Recently, the method of Keusch and O'Connell[6] has been used for testing the susceptibility of all anaerobic bacteria.

Results

Of the 123 patients with bacteremia due to *Bacteroides*, 41% were seen within the last 18 months of the study. Greater awareness of this potential threat to debilitated surgical patients and to those receiving predisposing antibiotic therapy, as well as improved cultural techniques, may be among the factors responsible for this impressive increase in the incidence of *Bacteroides* bacteremia during this last decade.

Cultural Data

In 94 of the 123 patients (76.4%), *Bacteroides* alone was cultured from the blood, but in a significant number (29 of 123, 23.6%) polymicrobic bacteremia occurred simultaneously (Table 2). Other anaerobic bacteria, as well as several aerobic bacteria, were found associated with the *Bacteroides* bacteremia.

TABLE 2
Associated Bacteria Isolated in the 29 Cases of Polymicrobic Bacteremia

Organism	No. of cases
Staph. epidermidis	5
Staph. oureus	3
Group D streptococci	3
Escherichio coli	3
Peptococcus spp.	2
Peptostreptococcus spp.	2
Enterobocter spp.	2
Strep. mitis	1
Strep. mitis and *Staph. epidermidis*	1
Proteus spp.	1
Proteus spp. and *E. coli*	1
Group D streptococci and *E. coli*	1
Group D streptococci and *Strep. mitis*	1
Pseudomonos spp.	1
Bocteroides tunduliformis and *Clostridium histolyticum*	1
Staph. epidermidis and *Pseudomonos* spp.	1

In 36 of the patients (29.2%), *Bacteroides* were isolated from sites in addition to the blood. Postsurgical wounds or infected decubitus ulcers were the principal areas from which such isolation was made. Other isolates came from peritoneal fluid, lung abscesses, empyema, splenic abscesses, subphrenic space infections, pelvic abscesses, and vaginal discharges.

Some of the strains of *Bacteroides* were slow growers, as is characteristic of several members of the family Bacteroidaceae. Most of the isolates were identifiable within 14 days. The range was from only 48 hours in a few instances to 26 days in one instance. As previously advocated by several investigators,[7-10] including ourselves,[1] blood cultures should be incubated and monitored for a minimum of two weeks prior to considering them sterile.

During a two-month period in 1968, sufficient blood was drawn (15 ml) to inoculate the dextrose brain broth and the thiol and tryptic soy broths concurrently (5 ml per container). All three media were examined daily for two weeks, during which time eight sets of blood cultures grew *Bacteroides* spp. In three sets, the thiol broth only was positive; in four more sets, the thiol and tryptic soy broths were both positive; and in one additional set, all three media were positive (the thiol and tryptic soy broths within 48 hours and the dextrose brain broth at 10 days). The thiol and tryptic soy broths were then compared in parallel over a 10-month period. Again, the bottles were examined daily for two weeks. A total of 40 blood cultures grew *Bacteroides* spp., of which 18 were positive in both media, 11 in thiol broth only, and 11 in tryptic soy broth only. The mean times for detection of positivity were 4.8 and 6.8 days in tryptic soy broth and thiol broth, respectively—differences that are not statistically significant.

Clinical Data

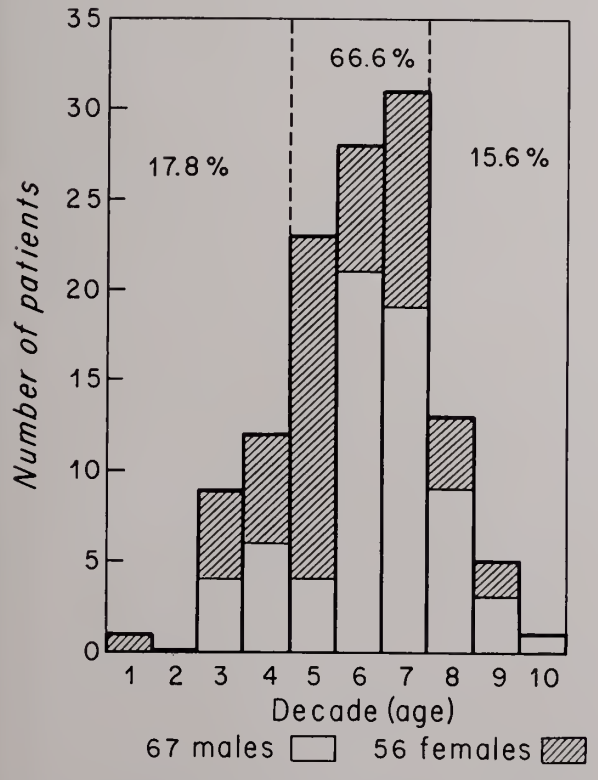
Patient Age.—Sixty-seven males and 56 females were included in the group (Figure). Ages ranged from eight and a half years to 93 years, with a mean of 56 years. Eighty-two patients (66.7%) were between 41 and 70 years old; 22 (17.9%) were younger than 40; and 19 (15.4%) were older than 70.

Underlying Problems.—All patients had un-

derlying conditions. Seventy-six (61.8%) had gastrointestinal lesions; 22 (17.9%), genitourinary problems; and 25 (20.3%), miscellaneous problems.

The most common underlying gastrointestinal problem was a malignant process involving the colon (21 patients). Other diseases of the colon included diverticulitis (eight patients), polyps (five), and chronic ulcerative colitis (two).

Nine patients had diseases of the small bowel. These included lymphoma, carcinoid tumor, jejunal ulcer, obstruction, intestinal perforation, gastrojejunocolic fistula, leiomyoma, post-gastrojejunostomy, and multiple fistulae. Nine patients had some type of hepatobiliary tract disease prior to the onset of bacteremia. Seven had pancreatic diseases: five, acute or chronic pancreatitis; one, carcinoma of the head of the pancreas; and one, Zollinger-Ellison syndrome. Three patients had gastric abnormalities: one, gastrojejunal ulcer; one, regurgitative alkaline gastritis; and one, carcinoma of the stomach. Three patients had esophageal problems. Eight had miscellaneous gastrointestinal problems such as trauma, duodenal ulcer, acute appendicitis, and rectal prolapse.



Figure—Distribution by sex and decade of patients with *Bacteroides* bacteremia.

Genitourinary problems were present in 22 patients. Sixteen had underlying gynecologic disease; in more than half, the disease was malignant. Of the remaining six patients with urologic problems, three had malignancies.

The 25 patients with miscellaneous underlying problems had diseases such as those of the skin and subcutaneous tissues, cardiovascular system, hematopoietic system, central nervous system, skeleton, and connective tissue, so-called fever of unexplained origin, and drug addiction.

Precipitating Factor

In 101 patients, a diagnostic or surgical procedure shortly preceded the bacteremic episode and was believed to represent a significant causal relationship. Gastrointestinal operations or procedures, uro-gynecologic manipulations, and other surgical techniques antedated the bacteremia in 78, 13, and 10 patients, respectively.

Eighty-nine patients had clinical evidence of *Bacteroides* bacteremia within three weeks of the diagnostic or surgical procedure (Table 3).

TABLE 3
Lag Phase Between Precipitating Factor and Onset of Symptoms in *Bacteroides* Bacteremia

Time	Cumulative number of patients	Cumulative percentage
Within 24 hr	26	21.1
Within 1st week	65	52.8
Within 2nd week	87	70.7
Within 3rd week	89	72.4
More than 3 weeks	34	27.6

Portal of Entry

The portal of entry remained indeterminate in only nine cases. The gastrointestinal route was presumed to be the portal in 56 cases. Wound infection was thought to be the portal in 38 other cases; in 33 of these, infection occurred after intra-abdominal surgery. In six patients with decubitus ulcers, the skin was presumed to be the portal. Other sites of entry included the female pelvis (11 cases), urinary tract (one case), spleen (one case), and respiratory tract (one case).

Signs and Symptoms

Bacteremia due to *Bacteroides* manifested itself most commonly by a febrile reaction of abrupt onset occurring during the late postoperative period. Profuse sweating, chilly sensations or shaking chills, abdominal distention with a so-called silent abdomen, anorexia, nausea, and vomiting were frequently present. Not uncommonly the patient complained of extreme fatigue and weakness. In about 75% of patients spiking fever was present. In others a remittent fever or even a low-grade fever was observed. Only four patients had oral temperatures of 100 F or less during the bacteremic episode. The highest temperature was 107 F (rectal); the average was 103 F (oral).

The incidence of other features of bacteremia due to *Bacteroides* included shock (25%), metastatic abscesses (22.7%), pneumonitis (16.1%), foul-smelling drainage (13.7%), clinically detectable jaundice (10%), diarrhea occurring prior to antibiotic therapy and stopping with control of infection (8%), and acute thrombophlebitis (4.7%).

Twenty-seven patients (21.9%) had central nervous system manifestations. These included mental clouding (six patients), coma (four), marked apprehension (three), lethargy (three), dizziness (three), restlessness (two), hallucinations (two), euphoria and delirium (one), toxic psychosis (one), headache (one), and hemiplegia (one).

Supraventricular tachycardia was noted in two patients.

Consumption coagulopathy and the syndrome of inappropriate secretion of antidiuretic hormone were detected in one patient each.

Sixty-eight patients (more than 50%) were receiving or had received one or several antibiotics, the most common regimen being a combination of penicillin G and streptomycin given parenterally during the postoperative period.

Finally, 17 patients had received a so-called preoperative bowel preparation, usually including neomycin or bacitracin.

Laboratory Data

Besides microbiologic information, other laboratory data were not specific for *Bacteroides* infection but were compatible with many other bacterial diseases. Anemia, when present, was normocytic and normochromic, and its severity appeared to reflect the duration of the illness and the nature of the underlying disease. Leukocytosis and neutrophilia were noted in most of the patients. Leukocyte counts varied from 10,000 to 61,000/cu mm, with an average of 15,000. A leukemoid reaction was seen in five cases. The erythrocytic sedimentation rate (Westergren method) was regularly elevated, and values above 100 mm in one hour were not uncommon. Roentgenograms of the thorax revealed a nonspecific pneumonitis in 16.1% of cases.

TABLE 4
Types of Therapy and Outcome in *Bacteroides* Bacteremia

Treatment	No. of patients	No. of cures	No. of deaths
Surgical drainage with antibiotic	49	38	11
A tetracycline	21	18	3
Chloramphenicol	11	10	1
Penicillin G or ampicillin	4	2	2
Erythromycin	4	3	1
Cephalothin	9	5	4
Antibiotic without drainage	39	26	13
A tetracycline	20	13	7
Chloramphenicol	5	1	4
Penicillin G or ampicillin	6	6	0
Erythromycin	2	2	0
Cephalothin	6	4	2
Surgical incision and drainage	19	16	3
No drainage and no antibiotic	16	8	8
Total	123	88 (71.5%)	35 (28.5%)

Treatment and Outcome

Because of a lack of uniformity in the mode of therapy, specific conclusions in regard to the effectiveness of individual regimens are hazardous to make. Inappropriate choice of antibiotics, inadequate dosage of the drug or drugs chosen, delayed onset of therapy, severity of underlying disease, presence of bacteremic shock, and metastatic suppuration are some of the factors that make evaluation of therapy difficult.

Patients were divided into four groups according to the regimen employed and the results obtained (Table 4).

Of the 123 patients, the largest number (49 patients) underwent surgical drainage in addition to antibiotic therapy; 38 patients were cured and 11 died. Of a group of 39 patients receiving antibiotics only, without debridement or drainage, 26 survived and 13 died. Surgical incision and drainage was the only mode of therapy in a group of 19 patients, of whom 16 survived and only three died. The patients who received drainage without antibiotic therapy were less ill than those who received both forms of treatment. Antibiotic therapy was not given to these patients, because their fever, chills, and tachycardia rapidly subsided after surgical drainage, and they appeared well before the report of the positive blood cultures became available. Finally, of 16 patients in whom neither antibiotic therapy nor surgical drainage was used, eight were cured and eight died.

Several antibiotics were used in the treatment: a tetracycline, chloramphenicol, a penicillin, erythromycin, and cephalothin. Antibiotic susceptibility tests were not carried out routinely until recently, and values for minimum inhibitory concentrations (MIC) are shown in Table 5.

These susceptibility studies demonstrated that all 24 strains tested were sensitive to 25 μg or less of a tetracycline or chloramphenicol. These two antibiotics have been considered over the years to be the agents of choice in the treatment of *Bacteroides* infection.[1,7-9] Other investigators have reported similar data.[11-13] Except for *Bacteroides fragilis,* which is usually resistant to the penicillins, ampicillin, and cephalothin, the other members of the Bacteroidaceae family are susceptible in vitro to these antibiotics.[6] Ingham and co-workers[14] recently reported somewhat different data after studying the in-vitro susceptibility of 35 strains of *B. fragilis* isolated from a group of 115 patients. Using the agar-dilution method, they found that all strains were resistant to streptomycin, neomycin, and polymyxin, slightly sensitive to penicillin G and ampicillin, and fully sensitive to tetracycline, chloramphenicol, erythromycin, and lincomycin. The minimum bactericidal concentrations of chloramphenicol, erythromycin, or lincomycin were two to four times their minimum inhibitory concentrations. The tetracyclines failed to exert any consistent bactericidal effect. More investigations on the clinical value of lincomycin and erythromycin are needed. Our in-vitro data indicate that 16 of 21 strains of *B. fragilis* were inhibited by 6.25 μg or less of erythromycin.

TABLE 5

Antibiotic Susceptibility of *Bacteroides fragilis*[6] (Cumulative Number of Strains) in *Bacteroides* Bacteremia

Antibiotic	No. of strains	Concentration of μg/ml							
		0.78	1.56	3.12	6.25	12.5	25	50	100
Penicillin G	24	1	2	2	4	10	19	22	24
Erythromycin	21	0	2	11	16*	16	19	20	21
Tetracycline	24	3	8	9	11	16	24†	....	....
Cephalothin	17	0	0	0	0	0	3	6	17
Chloramphenicol	24	0	0	2	7	23	24‡	....	....
Ampicillin	7	0	0	0	0	2	4	5	7
Streptomycin	2	0	0	0	0	0	0	0	0
Kanamycin	2	0	0	0	0	0	0	0	0
Gentamicin	1	0	0	0	0	0	1	....	....

*16 of 24 strains inhibited by 6.25 μg or less/ml of erythromycin.

†24 of 24 strains inhibited by 25 μg or less/ml of tetracycline.

‡24 of 24 strains inhibited by 25 μg or less/ml of chloramphenicol.

Discussion

The classification of the family Bacteroidaceae has been subject to considerable disagreement. Schemes of classification range from the detailed descriptions of Prévot[15] and of Smith and Holdeman[4] to the more simplified approach of Rosebury,[2] which is based primarily on fermentative and growth patterns. Other characteristics, as outlined by Dowell and Hawkins,[5] also appear to fit the patterns of the described species. Finegold and associates[13] have pointed out that antibiotic susceptibility patterns may provide additional useful information to the morphologic and biochemical criteria used for classification and characterization of these bacteria.

Anaerobic infections in general and *Bacteroides* infections in particular may be more frequent than realized. As early as 1897 French investigators[16,17] reported these agents as etiologic pathogens. Suppurative lesions involving the appendix and the female pelvis were then described by these authors.

Animal infections due to *Bacteroides* had been reported earlier by Loeffler[18] in the German literature. He then successfully produced necrotic lesions in mice after subcutaneous inoculation with purulent material obtained from diphtheritic calves.

In man, the true incidence of *Bacteroides* infection is unknown. In general, the pathogenicity of *Bacteroides* appears to be low; but under certain circumstances, these organisms may act as opportunists and cause serious diseases. Failure to obtain anaerobic bacterial cultures, the slow-growing properties of these bacilli, the premature discarding of apparently negative cultures, or the use of inappropriate culture media may contribute to the failure of detecting *Bacteroides* infection.

Despite these difficulties, several papers in recent years have described many human infections due to *Bacteroides*.[7-9,19-23] Any human tissue organ may be involved. Suppurative lesions and putrid or foul-smelling abscesses are not uncommon. Patients with chronic otitis, with or without central-nervous-system involvement, were described at the beginning of this century by Rist.[24] More recently Smith and associates,[25] Lifshitz and associates,[26] Salibi,[27] and Schoolman and co-workers[20] outlined some of the diagnostic challenges and therapeutic difficulties involved with the infections of the central nervous system. Cases of pharyngitis and tonsillitis have been reported.[28] The spectrum of diseases due to *Bacteroides* is completed by the reports involving pneumonia, lung abscess, empyema,[29-32] subacute bacterial endocarditis,[7,10,33] liver abscesses,[34-37] peritonitis,[35] diverticulitis,[38] pyelonephritis,[39] superficial and deep pelvic abscesses,[40] endometritis,[41] osteomyelitis,[42] musculoskeletal infections,[43] cholecystitis and suppurative lesions after surgical treatment of gastrointestinal malignancies,[22] and other surgical procedures.[8]

Bacteroides bacteremia may express itself in many different ways, varying from asymptomatic forms to forms that cause rapid deterioration and death.[1,7,9,19,23,38,44-46] Although less severe clinical forms are more regularly encountered, only four of our patients had a relatively asymptomatic form of the infection. Three of them survived without any specific therapy; the other died of diffuse abdominal carcinomatosis. Most of our patients had manifestations of *Bacteroides* bacteremia similar to those seen in bacteremia caused by other gram-negative organisms. In the detection of *Bacteroides* bacteremia, a high index of suspicion and knowledge of the potential pathogenicity of this organism are very important. The sudden development of chills, fever, and sweats in a patient convalescing from a colectomy performed for a malignant tumor, especially in the presence of an infected abdominal wound, should alert one to the possibility of *Bacteroides* bacteremia.

The high incidence of patients receiving antibiotics when the bacteremia develops, as was demonstrated in 68 of our patients, should call attention to the importance of this predisposing condition.

The preoperative cleansing of the bowel with a drug such as neomycin may alter the normal flora of the bowel which appears to create a favorable milieu for rapid growth of *Bacteroides*. Seventeen of our patients had received such preparations.

All of our patients had some underlying noninfectious disease. Gastrointestinal problems were the most common (61.7%), followed by genitourinary (17.0%) and miscel-

laneous problems (21.3%). Both sexes were equally affected. In our experience, *Bacteroides* bacteremia appears to be rare in patients who are less than 15 years old. In the present series, only one boy, 8½ years of age, had *Bacteroides* bacteremia. Most patients between the ages of 20 and 40 years with *Bacteroides* bacteremia reviewed in this study were patients with gynecologic disorders.

Bacteroides bacteremia occurred after a surgical or diagnostic procedure in more than 80% of our cases. In 72.3% of them, evidence of bacteremia occurred within three weeks of the precipitating factor.

Gastrointestinal operations or procedures involving the colon had been performed in 52 of our patients (42.3%).

The portal of entry was determined in 91% of the cases; the gastrointestinal tract, wound infections after abdominal surgery, the female pelvis, and skin infections (decubitus ulcer) were the four most common portals of entry in our patients. In no case was the oropharynx considered a portal of entry in our series, in contradistinction to Lemierre's findings in 1936.[28]

Cardiovascular collapse with secondary oliguria was of serious prognostic significance. Bacteremic shock occurred in 31 of our patients, for an incidence of 25%. Nineteen of these patients died despite intensive therapy.

Symptoms and signs of metastatic infective lesions have been reported as being characteristic of *Bacteroides* infection.[19] They were diagnosed in 28 of our cases, with documented cultures present in 12.

Malodorous wound drainage occurred in 17 patients (13.8%); frequent loose stools antedating antibiotic therapy and disappearing with control of the infection were noted in 10 patients (8.1%); jaundice occurred in 12 patients (9.8%); and acute thrombophlebitis was observed in six others.

Thirty-five patients died from uncontrolled infection for an overall mortality rate of 28.5%, which is comparable to that of our previous report.[1] Other investigators[9] have reported a mortality rate of 20% in a series of 25 patients, of whom nine (36%) were less than 30 years old.

The advent of antimicrobial drugs has significantly improved the prognosis for most patients with bacteremia due to *Bacteroides*, when compared to the mortality rate of 83% found in the presulfonamide era, as determined by Gunn.[19] On the basis of our past experience and that of others, we have considered a tetracycline (tetracycline, oxytetracycline, or chlortetracycline) as the drug of choice for the treatment of bacteremia due to *Bacteroides*. Intravenous administration of 500 mg of tetracycline or oxytetracycline every six hours is begun as soon as possible in most cases. However, oral administration of 500 mg of one of the tetracyclines every six hours has been successful in some cases. (Oral dosage applies only to the tetracyclines noted, that is, tetracycline, oxytetracycline, or chlortetracycline.) The likelihood of either hepatotoxicity or nephrotoxicity may lead to the use of chloramphenicol in place of a tetracycline, in spite of the possibility of drug-induced bone-marrow depression.[47-49] As already mentioned, other workers have recommended use of either erythromycin or lincomycin for treating infections due to *B. fragilis*.[14] Our data seem to indicate that other antibiotics, including penicillin G, ampicillin, and cephalothin, are also effective in the management of selected cases of *Bacteroides* bacteremia.

Our custom has been to initiate antibiotic treatment empirically after procurement of blood cultures in seriously ill patients and to modify the antibacterial regimen later if cultural reports and the patient's condition warrant. Antibacterial therapy is continued for a minimum of two weeks. Blood cultures should be rechecked after completion of therapy to verify permanent eradication of the anaerobic bacilli. In contradistinction to these generalizations, some of our patients recovered without the use of antimicrobial therapy.

Every effort should be made to examine surgical wounds and decubitus ulcers daily. Any suggestion of gross, and particularly malodorous, infection should alert the physician to the possibility of anaerobic wound infection, and appropriate specimens should be obtained and cultured specifically for anaerobic organisms. Persistent fever or lack of improvement in the general condition of the patient should immediately signal the possibility of an occult intracavitary abscess. Surgical incision and drain-

age is an essential measure in the treatment of many *Bacteroides* infections.

The increase in incidence of *Bacteroides* bacteremia at the Mayo Clinic from 11 cases in the decade of February 1949 to February 1959 to 123 in the current decade is impressive.

Summary

Data on 123 patients with bacteremia due to *Bacteroides* are presented. All patients had debilitating underlying conditions. Surgical procedures on the colon had been performed within three weeks of the onset of the bacteremia in 43% of these patients. In 29.2% of patients, *Bacteroides* was also isolated from sites other than the blood and mainly from abdominal wounds after gastrointestinal surgery. The sudden onset of chills, fever, and severe diaphoresis during the postoperative course of a patient prepared for colon surgery with neomycin or similar drugs, or one receiving antibiotics for other reasons, requires consideration of the possible presence of *Bacteroides* bacteremia. Another clue to *Bacteroides* infection is the presence of a foul-smelling exudate from which organisms fail to grow on aerobic plates.

Persistently negative blood cultures despite a continued febrile course of the patient should prompt the physician to ensure that anaerobic blood cultures have been obtained.

Anaerobic blood cultures should be observed for a minimum of two weeks before they can be considered negative for *Bacteroides*.

Polymicrobic infections were noted in 23.6% of the patients in this series. Early diagnosis, severity of underlying disease, treatment with an appropriate antibiotic for a minimum of 14 days, and recognition and drainage of suppurative foci are significant factors that affect the prognosis of this more frequently occurring infection. In our experience, the incidence of *Bacteroides* bacteremia has increased more than 10-fold over the last decade.

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Make the most of yourself, for that is all there is of you.—Ralph Waldo Emerson.

Nothing is to wonderful to be true.—Faraday.



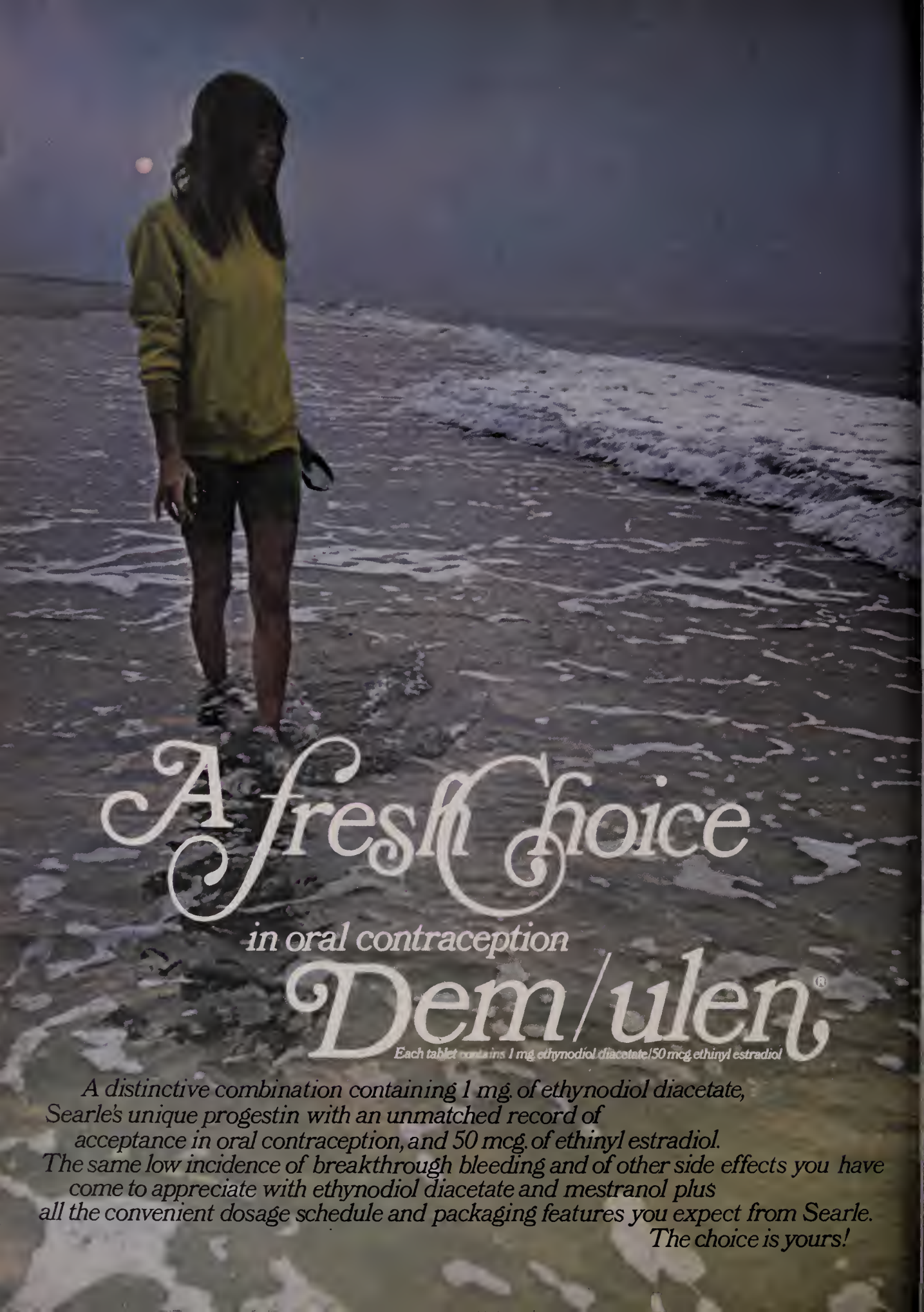
CALORIES / 7 oz. Serving*

Beef Broth	22	Vegetable	68
Consommé	29	Tomato	69
Chicken with Rice	43	Cream of Asparagus	70
Chicken Gumbo	48	Cream of Chicken	76
Chicken Noodle	54	Cream of Mushroom	115
Cream of Potato	58	Green Pea	116
Chicken Vegetable	60	Cream of Shrimp (Frozen)	132
Vegetable Beef	66	Bean with Bacon	133

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Actions—Demulen acts to prevent ovulation by inhibiting the output of gonadotropins from the pituitary gland. Demulen depresses the output of both the follicle-stimulating hormone (FSH) and the luteinizing hormone (LH).

Special note: Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. Both types provide almost completely effective contraception.

An increased risk of thromboembolic disease associated with the use of hormonal contraceptives has now been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure, liver disease and reduced tolerance to carbohydrates, have not been quantitated with precision. Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency of some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can be neither affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.



Indication—Demulen is indicated for oral contraception.

Contraindications—Patients with thrombophlebitis, thromboembolic disorders, cerebral apoplexy or a past history of these conditions, markedly impaired liver function, known or suspected carcinoma of the breast, known or suspected estrogen-dependent neoplasia and undiagnosed abnormal genital bleeding.

Warnings—The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism and retinal thrombosis). Should any of these occur or be suspected the drug should be discontinued immediately.

Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism, and cerebral thrombosis and embolism and the use of oral contraceptives. There have been three principal studies in Britain[1-3] leading to this conclusion, and one[4] in this country. The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about sevenfold, while Sartwell and associates[4] in the United States found a relative risk of 4.4, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as nonusers. The American study also indicated that the risk did not persist after discontinuation of administration, and that it was not enhanced by long-continued administration. The American study was not designed to evaluate a difference between products. However, the study suggested that there might be an increased risk of thromboembolic disease in users of sequential products. This risk cannot be quantitated, and further studies to confirm this finding are desirable.

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions medication should be withdrawn.

Since the safety of Demulen in pregnancy has not been demonstrated, it is recommended that for any patient who has missed two consecutive periods pregnancy should be ruled out before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule the possibility of pregnancy should be considered at the time of the first missed period.

A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time.

Precautions—The pretreatment and periodic physical examinations should include special reference to the breasts and pelvic organs, including a Papanicolaou smear, since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals. Endocrine and possibly liver function tests may be affected by treatment with Demulen. Therefore, if such tests are abnormal in a patient taking Demulen, it is recommended that they be repeated after the drug has been withdrawn for two months. Under the influence of progestogen-estrogen preparations preexisting uterine fibromyomas may increase in size. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam adequate diagnostic measures are indicated. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. Any possible influence of prolonged Demulen therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving Demulen therapy. The age of the patient constitutes no absolute limiting factor, although treatment with Demulen may mask the onset of the climacteric. The pathologist should be advised of Demulen therapy when relevant specimens are submitted. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids.

Adverse reactions observed in patients receiving oral contraceptives—A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions: thrombophlebitis, pulmonary embolism and cerebral thrombosis.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions; neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, breast changes (tenderness, enlargement and secretion), change in weight (increase or decrease), changes in cervical erosion and cervical secretions, suppression of lactation when given immediately post partum, cholestatic jaundice, migraine, rash (allergic), rise in blood pressure in susceptible individuals and mental depression.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: anovulation post treatment, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption and itching.

The following laboratory results may be altered by the use of oral contraceptives: hepatic function: increased sulfobromophthalein retention and other tests; coagulation tests: increase in prothrombin, Factors VII, VIII, IX and X; thyroid function: increase in PBI and butanol extractable protein bound iodine, and decrease in T^3 uptake values; metyrapone test and pregnanediol determination.

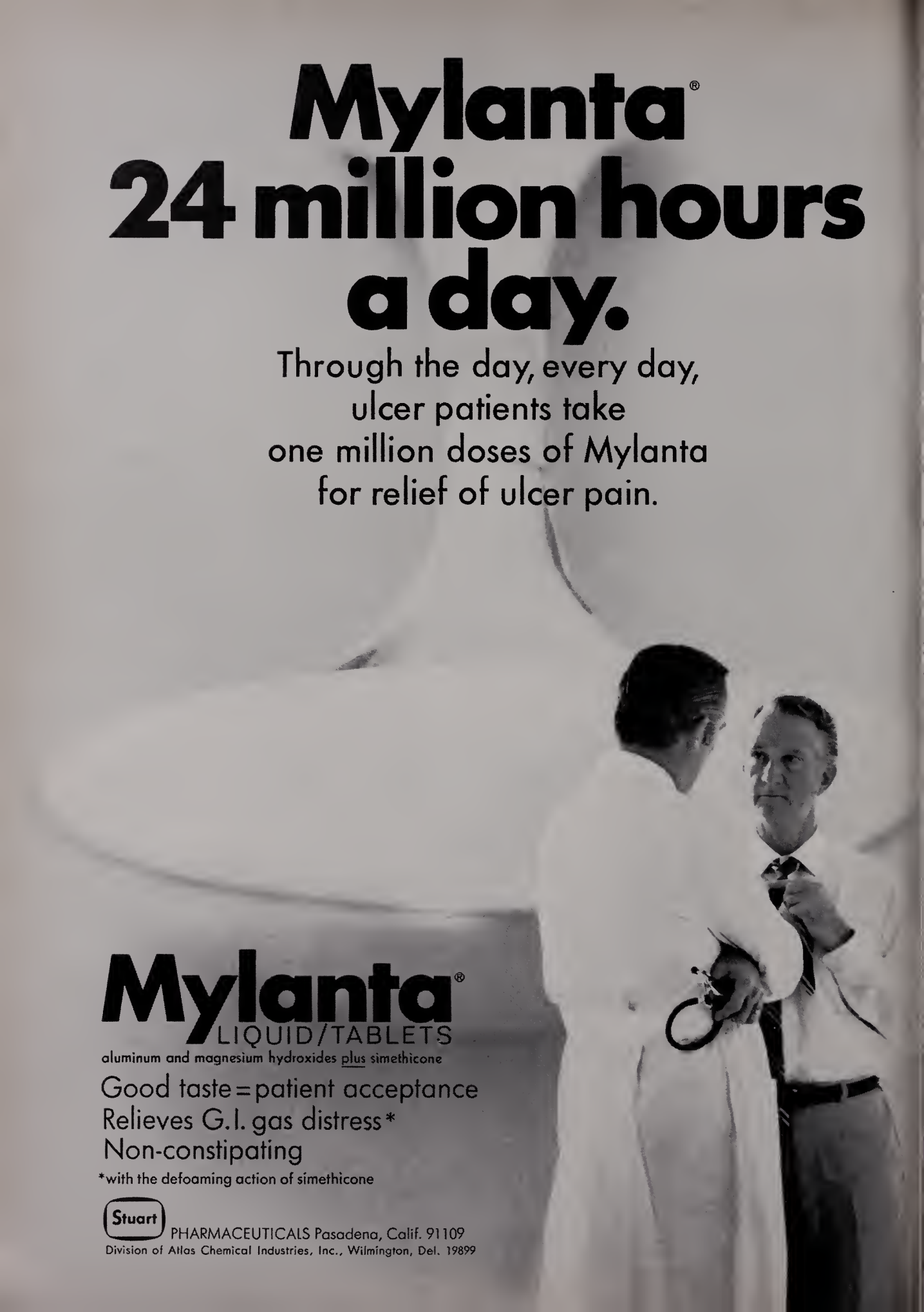
References: 1. Royal College of General Practitioners: Oral Contraception and Thrombo-Embolic Disease, J. Coll. Gen. Pract. *13*: 267-279 (May) 1967. *2.* Inman, W. H. W., and Vessey, M. P.: Investigation of Deaths from Pulmonary, Coronary, and Cerebral Thrombosis and Embolism in Women of Child-Bearing Age, Brit. Med. J. *2*:193-199 (April 27) 1968. *3.* Vessey, M. P., and Doll, R.: Investigation of Relation Between Use of Oral Contraceptives and Thromboembolic Disease. A Further Report, Brit. Med. J. *2*:651-657 (June 14) 1969. *4.* Sartwell, P. E.; Masi, A. T.; Arthes, F. G.; Greene, G. R., and Smith, H. E.: Thromboembolism and Oral Contraceptives: An Epidemiologic Case-Control Study, Amer. J. Epidem. *90*:365-380 (Nov.) 1969.

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Editorials

The Enema Can Be A Dangerous Act

THE PAPER IN a recent issue of MINNESOTA MEDICINE by Dr. D. G. McQuarrie* entitled *The Curious Clysters* is at once timely and significant. Cases such as Dr. McQuarrie's are not rare; people often do odd things and suffer the consequences thereof. The persons committing these "strange" acts are often otherwise very intelligent persons who in most instances are environmentally competitive and therefore "normal." One recalls the case of a man who did not enjoy the taste of alcoholic beverages but wished to experience the effects and "be one of the boys" at a party. He instilled grain alcohol into his rectum and developed a very severe proctitis.

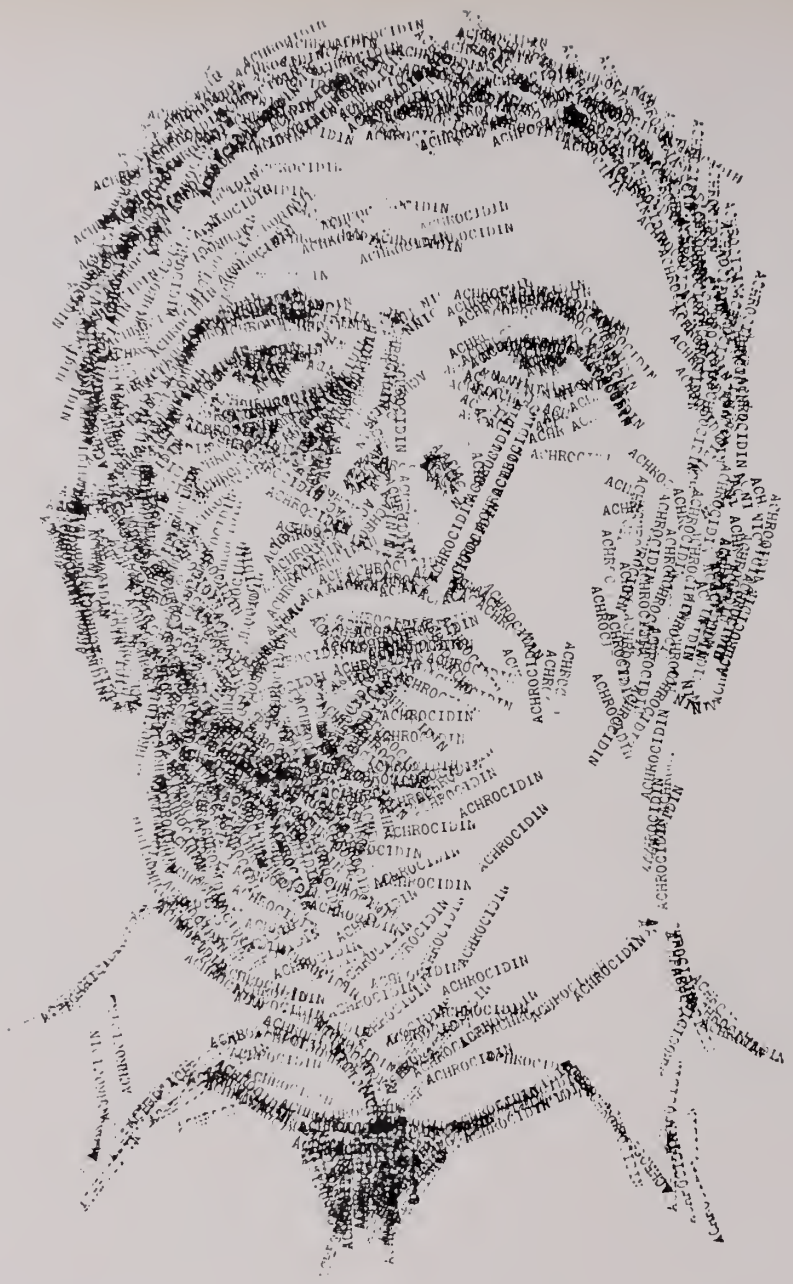
A garage mechanic, aware of the virtues of lubricating oil for an automobile engine, decided to take an enema of automobile lubricating oil for his own mechanism and suffered an irreversible transmural proctitis which produced a fibrous stricture of his rectum necessitating a permanent colostomy.

On a rainy night a business man, while at his lake home, felt the need of an enema and took it in the squatting position. A loud peal of thunder made him lose his balance; he fell backwards and the enema tip perforated his anterior rectal wall. The squatting position is certainly not one to be recommended.

The literature is replete with published reports of iatrogenic incidents resulting from enemas: perforation by the enema tip, laceration of the rectal wall from the pressure of a barium enema balloon, perforation of a weakened area of the colon from the hydrostatic pressure of a barium enema, necrosis of the liver following a tannic acid and barium mixture in an enema, water intoxication from an enema, and severe necrosing proctitis from too strong a solution of hydrogen peroxide in an enema. Such cases should alert all of us to the potential hazards of enemas, chemically, toxicologically and mechanically.

There are two practices which should be condemned. The first is the use of soap suds in cleansing enemas. This practice has been handed down from one generation of physicians to the next in the same traditional manner that many customs were handed down in the play, Fiddler on the Roof. Soap is a strong chemical cleansing agent which is fine for non-living fabrics, hard surfaces, and the skin of the human body. It has no place on the delicate mucous membranes inside the body. A soapsuds enema will not accomplish emptying of the lower alimentary canal any better than will tap water or saline solutions. The custom of giving soapsuds enemas has been abandoned in many hospitals.

*McQuarrie, D. G.: The Curious Clysters. Minnesota Med 53:727, 1970.



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Contraindications: Hypersensitivity to any component.

Warning: In renal impairment, since liver toxicity is possible, lower doses are indicated; during prolonged therapy consider serum level determinations. Photodynamic reaction to sunlight may occur in hypersensitive persons. Photosensitive individuals should avoid exposure; discontinue treatment if skin discomfort occurs.

Precautions: Drowsiness, anorexia, slight gastric distress can occur. In excessive drowsiness, consider longer dosage intervals. Persons on full dosage should not operate vehicles. Nonsusceptible organisms may overgrow; treat superinfection appropriately. Treat beta-hemolytic streptococcal infections at least 10 days to help prevent rheumatic fever or acute glomerulonephritis. Tetracycline may form a stable calcium complex in bone-forming tissue and may cause dental staining during tooth development (last half of pregnancy, neonatal period, infancy, early childhood).

Adverse Reactions: *Gastrointestinal*—anorexia, nausea, vomiting, diarrhea, stomatitis, glossitis, enterocolitis, pruritus ani. *Skin*—maculopapular and erythematous rashes; exfoliative dermatitis; photosensitivity; onycholysis, nail discoloration. *Kidney*—dose-related rise in BUN. *Hypersensitivity reactions*—urticaria, angioneurotic edema, anaphylaxis. *Intracranial*—bulging fontanels in young infants. *Teeth*—yellow-brown staining; enamel hypoplasia. *Blood*—anemia, thrombocytopenic purpura, neutropenia, eosinophilia. *Liver*—cholestasis at high dosage.

Upon adverse reaction, stop medication and treat appropriately.

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The second practice to be condemned is the vertical position. Though medical corpsmen in some military installations are still being taught to give enemas with the patient standing up and leaning against the bathroom wall this is an extremely dangerous method, as the anterior rectal wall can easily be perforated. Patients with coronary disease have gone on to collapse and death following this kind of enema. Hence constant care should be exercised in the manner in which the "deadly enema"* should be given.

William C. Bernstein, M.D.
Minneapolis, Minnesota

*New Engl J Med, January 23, 1964.
†Department of Surgery, University of Minnesota.

Through a (Shot) Glass Darkly

ANOTHER VOICE is crying in the wilderness. Doctors Jerome R. Hanson and John N. Simons* raise their voice elsewhere in this journal to tell us that in Minnesota, as in experience countrywide, alcohol contributes to the tragedy of highway accidents. In some ways, theirs is a pathetic article.

Please understand. Their effort and their vision are not pathetic; they are lighting the way for the rest of us. Their report is pathetic because of handicaps imposed on it before it was born, by a society which refuses to recognize alcoholism as a treatable disease. These authors sought to learn and to prove what contribution alcohol actually made to the tragic accidents they had to care for; but they were forced to deal in hearsay and presumption. As dramatic as their conclusions are, I believe they would be magnified, had factual measurements of blood alcohol been included in these records.

Why do doctors refuse to study blood alcohol, while they delight in studying a host of other chemical measurements of disease? Surely we are smart enough to distinguish between "medical" and "legal" tests. The "implied consent" rule applies only to the determination of blood alcohol obtained at the request of an arresting police officer and performed in a government laboratory. In contrast, the treating physician automatically has consent to measure blood alcohol in his own laboratory for medical purposes, exactly as he would measure blood sugar.

So why *should* he do it? Because he can't recognize elevated blood alcohol by examination alone? Because he can't separate the effect of exposure, confusion, blood loss, or head injury? Because he might assume alcoholism and miss intoxication with another drug? Because blood alcohol levels of 100 mg % or more are not seen in social drinking? These levels represent serious, heavy drinking, and *identify* the real alcoholic. Alcoholism is a progressive disease, which medicine has never yet recognized in its early stages before it becomes truly destructive.

It just isn't enough for a doctor to treat an accident victim and miss or ignore the accompanying diagnosis of alcoholism. Any physician treating an accident victim is obliged to make diagnoses of concomitant diseases: diabetes, coronary sclerosis, penicillin allergy. Alcoholism is such a disease, susceptible of diagnosis, and responsive to modern-day coordinated treatment forms.

Physicians must at last recognize alcoholism. We must subject it to clinical discipline and objective laboratory analysis. We must hasten the day when studies like this one of Doctors Hanson and Simons will be freed of artificial handicaps, and will have facts to deal with.

S. R. Maxeiner, Jr., M.D.†
Minneapolis, Minnesota

*Hanson, J. R. and Simons, J. N.: Alcohol-Related Highway Accidents. Minnesota Med 53:905, 1970.
†Chairman, Committee on Automotive Injuries, Minnesota State Medical Association.

Editor's Note: "Through a Glass Darkly": Corinthians I, 13:12: "For now we see through a glass, darkly; but then face to face: now I know in part; but then shall I know even as also I am known." A bit cryptic, perhaps, but meaning that in the future our vision will so broaden and deepen as to clarify what may now be only vague and hazy; or perhaps Omar Khayyam's one line: "There was the Veil through which I might not see."

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You May Be Right

Budget

I THANK YOU for this opportunity to respond to Doctor Recht's letter. I shall begin by saying that his letter forthrightly and fairly sums up the thinking of the House of Delegates. I shall end by pointing out that this issue illustrates what I said in the editorial: MINNESOTA MEDICINE cannot be a scientific journal of any substance without an adequate budget.

Richard L. Reece, M.D.
Minneapolis, Minnesota

Responsibility

IF MINNESOTA MEDICINE is dying as alleged by Dr. Reece in his editorial in the July 1970 issue of MINNESOTA MEDICINE, let us ask where the responsibility belongs. Dr. Reece lays this responsibility on the House of Delegates of the Minnesota State Medical Association. These elected delegates voted to "cut the budget" of the Journal from $40,000 to $25,000. Why?

The income for MINNESOTA MEDICINE comes from subscriptions and advertising. The subscription price to members deducted from their dues is $7.50 per year. According to a May 1970 report by the Editor of MINNESOTA MEDICINE, the actual cost of publication to each member was $12.40 per year or according to Dr. Reece's editorial, $14.46 per year in addition to advertising revenue. The difference between the subscription price and the cost is paid from the general funds of the Minnesota State Medical Association. In spite of repeated strong recommendations by the Finance Committee of the Minnesota State Medical Association, MINNESOTA MEDICINE has not stayed within its budget. So, instead of approving an inflated budget of $40,000 or approximately $12.40 per member, the House of Delegates felt that only the income derived from the $7.50 member subscription price should be authorized. This amounts to approximately $25,000. All that the delegates asked was that MINNESOTA MEDICINE display fiscal responsibility.

More important, however, is the need to re-examine the role of MINNESOTA MEDICINE. Some of the questions asked by the House of Delegates are as follows: Is it actually serving as a primary source of scientific information for physicians of the state? Is it supplying important non-scientific and organizational news to member physicians? Is it an appropriate forum for the changes which involve medicine today? Is it worth the money which is spent on it? What basic need does it really fulfill? Should it be abolished and replaced by a bulletin as suggested by one resolution to the House of Delegates? Should it become part of a regional journal?

The House of Delegates, as elected representatives, voices the opinions of their colleagues and medical societies. They were not acting independently but exercised the responsibility given to them. I am sure that your answers to the above questions as well as further opinions from the medical profession in Minnesota will provide the delegates in 1971 aid in clarifying the future role of MINNESOTA MEDICINE.

Thomas M. Recht, M.D.
Minneapolis, Minnesota

Wisdom is the wealth of the wise.—W. G. Benham

YOU MAY BE RIGHT (Continued)

National Health Service

THERE ARE absolutely no grounds whatsoever to support the blanket statement contained in the President's Letter,* to the effect that the quality of medical care in the United Kingdom under the National Health Service has "diminished unmistakably." Many doctors seek to acquire maximum permissible lists simply and understandably to boost their annual income. Patients tend to call the doctor for trivia; until very recently the patient, not the doctor, was the arbiter of the need for medical care. One's friends and relatives in the profession can supply many illustrative examples of this, yet none would say that overall medical care has deteriorated. The trivial cases tend to be dealt with somewhat trivially. The other more serious cases are "passed on" to a higher medical (hospital) authority, perhaps too frequently. However, the outcome is that more patients are exposed to specialized hospital care which is second to none.

It is inconceivable that in the United Kingdom one would find a patient submitting to portacaval anastomosis by a surgeon who did not know the normal anatomical relationships between the portal vein and the inferior vena cava; yet I have seen this phenomenon in this country, where I have also seen a surgeon take four and a quarter hours to perform an emergency gastrectomy for a bleeding ulcer. During times of epidemic disease the general practitioner, both here and in the United Kingdom, tends to be swamped by long queues of patients.

There is no doubt that the individual British citizen—and more particularly the British employer—finds the taxes supporting the National Health Service extremely burdensome. The British are already the most highly taxed nation in the world. The extraordinarily impecunious state of the United Kingdom following World War II would have made it preferable—in the tradition of "The Mouse That Roared"—for Britain to have waged war against the United States and lost. The salvaging of Germany and Japan bears this out.

Yet it is well to remember that this altruistic legislation was initiated and promulgated by this struggling, devastated country in the face of overwhelming odds, not the least being the apathy and intransigence of the medical profession. The costs, high though they are, go towards defraying much more than the actual expense of medical care. The incapacitated person is paid unemployment insurance which may paradoxically be more than he earns at work. Our fellow citizens in this country are not above taking advantage of the British free-for-all system when visiting the United Kingdom—a state of affairs almost too ludicrous to envisage.

If the American Medical Association continues to oppose, for the right reason or none, legislation calculated to be for the overall improvement of health care as it has consistently done for the past 50 years, there is little doubt in my mind that a similarly imposed service will, in the not too distant future, be instituted in this country also. It would better befit the American Medical Association and its supporting state organizations to inquire most diligently into the means whereby a health plan formulated by the medical profession itself could be presented to the Government, so that the agony of arbitration and new legislation which the British National Health Service perpetually undergoes could be avoided in this country.

J. C. Campbell, M.D.
Albert Lea, Minnesota

*September, 1970, issue, page 937.

The Editor's Soliloquy

Must We Budget Progress?

HERE IS THE first of the Budget Issues.

When I took this job ten years ago—a job that has proven to be a full twenty-hour per week labor of love and professional dedication, interspersed within a fulltime practice of surgery—I was encouraged to develop a distinguished medical journal: one that would reflect the honorable and ethical practice furnished the public by the nonpareil physicians of Minnesota and the North Central States.

I have been proud of the achievements of our regional doctors, most of whom have been avid students of medical publications; and I am also proud of our Board of Editors who have secured for us both national and international recognition.

The policy of MINNESOTA MEDICINE has been to provide a wide variety of high-grade, up-to-date scientific material for the private practitioner, so that he may read it today and use it tomorrow, so to speak. In order to achieve our objective, it has been essential for the Board members who review manuscripts to be widely-read, well-versed, open-minded, and scientifically discriminating and critical of all articles to appear in MINNESOTA MEDICINE.

We have also included in the Journal a modicum of eclectic, non-technical matter to provide relief of sorts from rigid concentration, and designed to reflect and refract the imagery of medicine through the prism of time, place, and personality, be it that of doctor, patient, or observer.

As Editor-in-chief, I am striving to save MINNESOTA MEDICINE for the valuable asset it could well become in the near future, not only for our State but also for the entire North Central area, wherein at least one new medical school is now in prospect and where a few new teaching centers are also being drafted.

We doctors are not in need of discipline, en masse; of computerized evaluation, á la robot; or if a bureaucratic dictum under the subterfuge of peer review. We are in need, however, of maintaining our incorruptible independence and integrity and our peerless professional image. And if we do not elevate our medical literature to ever higher levels and maintain it thereon, rather than denigrating it to a pedestrian and parochial role, then, for our complacency and acquiescence, we may find ourselves totally and permanently subservient to officious and paralyzing bureaucracy.

Carl O. Rice, M.D.

Old Doc Hess says: Some people love, cherish, and guard their aches and pains.

—C.O.R.

Learning is like rowing upstream, not to advance is to drop back—Culinary Almanac.

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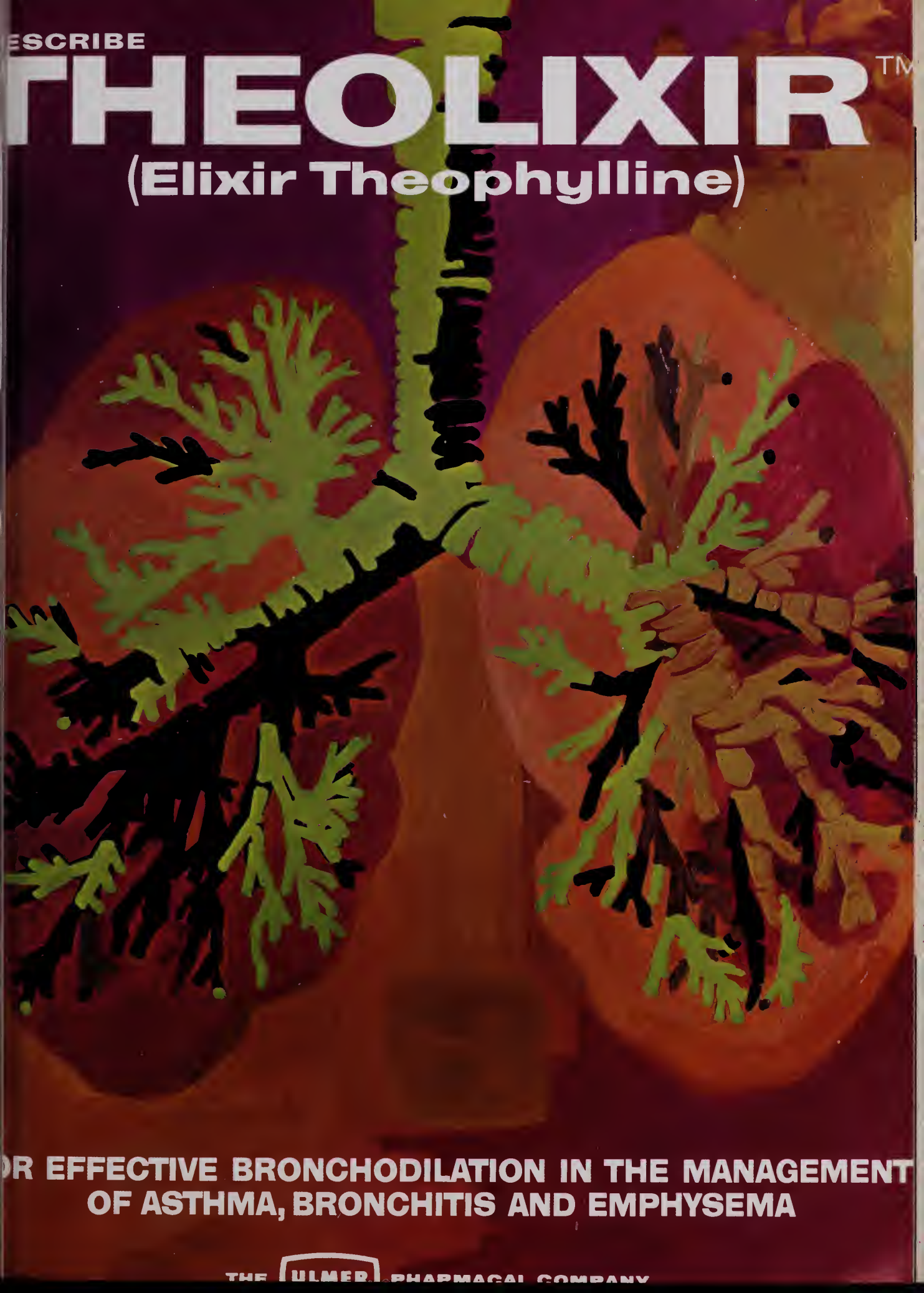
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(Continued to page 1201)


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(1) Ritchie, J. M., Central Nervous System Stimulants, in Goodman, L. S., and Gilman, A. (editors): The Pharmacological Basis of Therapeutics, New York, Macmillan Company, 1965, p. 363.

(2) Bickerman, H. A., Antiallergic Agents, In Modell, W. (ed.): Drugs of Choice 1966-1967, St. Louis, C. V. Mosby Company, 1966, p. 484.

(3) Miller, W. F., Emphysema, Treatment of Chronic Pulmonary, Postgraduate Medicine, March 1966, P230-239.

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Abstract

Liberalized Abortion*

The recent report of the Royal College of Obstetricians and Gynaecologists concerning their experience in England and Wales during the first year of liberalized abortion is of great interest. Due to the length of the article, much pertinent information has not been abstracted. To avoid misinterpretation, portions which are of special interest are quoted verbatim.

Prior to enactment of the Abortion Act the Council of the Royal College, because of "the desire to protect the interests of women," emphasized the "short-term and long-term hazards of terminating pregnancy." Their advice was only partially accepted. The Council stated that "induction of abortion is indicated only when, in the opinion of medical attendants, it is less dangerous to physical and mental health than continuation of the pregnancy. Abortion on social grounds alone, or on demand, was regarded as unethical and also undesirable from the standpoint of the women concerned."

A questionnaire was sent to all consultant obstetricians and gynaecologists employed in the National Health Service (N.H.S.) in England and Wales. Of 561 consultants, 80 percent completed and returned the questionnaire. The facts and opinions reported were based on 27,331 operations carried out in 233 departments of obstetrics and gynaecology during the first year after the Abortion Act came into force. The questions, answers and comments are reported in detail. Four hundred fifty consultants completed the questionnaire and 258 expressed additional views.

"The original protagonists for abortion law reform often argued that a large proportion of cases of spontaneous abortions hitherto treated in the hospital, and nearly all the associated deaths, were the result of criminal interference. Legalization of abortion would, they postulated, eliminate these. They brushed aside contrary arguments and evidence." The questionnaire showed that "despite a sharp rise in the number of notified therapeutic abortions from 1968 to 1969, there was not unfortunately any significant change in the number of cases of spontaneous abortion requiring admission to the hospital. Moreover, figures published by the Department of Health indicate that the number of fatalities associated with all types of abortion in England and Wales in 1968 was similar to that in previous years, and the figure for 1969 is expected to be only slightly lower."

"The risks of any of the currently available methods of terminating pregnancy, which involve general anaesthesia, have always been recognized by gynaecologists but have been dismissed by others as non-existent and imaginary." "Eight maternal deaths occurred in relation to 27,331 terminations of pregnancy during the year 1968-9. This gives a mortality rate of 0.3 per thousand, which is higher than the maternal mortality rate (including abortions, criminal or otherwise) for all pregnancies in England and Wales at the comparable time. A statement issued by the Secretary of State to Parliament on 4 February 1970 reveals a similar state of affairs in respect of about 54,000 induced abortions notified from all sources during 1969; among these there were 15 maternal deaths."

"Being aware of the immediate and remote hazards to maternal health, as well as to life, of termination of pregnancy, 80 percent of gynaecologists

*Contemporary Themes: The Abortion Act (1967). Findings of an Inquiry in the First Year's Working of the Act Conducted by the Royal College of Obstetricians and Gynaecologists. Brit Med J 30 May 1970, pp. 529-535.

take the view that the operation should be decided on and carried out only by consultant gynaecologists and their staff (para. 4). Their replies indicated that they considered that only in this way can women escape from the risks the presence of which they themselves cannot judge. Indeed, only an experienced gynaecologist can properly decide whether it is more dangerous in any case for pregnancy to continue than it is to induce abortion. And the need for such a decision is clearly laid down in the Abortion Act."

There is a great deal of variation of opinion concerning the wording of the Abortion Act. The problem is not in the wording but in its interpretation. The Act states that therapeutic abortion is legal only when two physicians decide that "certain defined medical indications justify it." "Legislators, the Press and a small group of agitators have, ever since the enactment, fostered the idea that it provides for abortion on demand, or for social or economic reasons alone." "Even the Secretary of State for Health and Social Services recently expressed his satisfaction about the fact that the Act had, during 1969, prevented the birth of 20,000 illegitimate children in this country. There is nothing in the Act to indicate that the extramarital nature of a conception in itself provides an acceptable indication for termination of pregnancy."

Prior to passage of the Abortion Act, the advocates for liberalizing the abortion law repeatedly assured the Houses of Parliament that they did not advocate abortion on demand. It is unlikely that the Act would have become a law had this been the case. There has been a "campaign" which has resulted in the belief that any woman has a right to a therapeutic abortion and that gynaecologists are obligated "to apply their surgical skills when told and irrespective of their expert judgment." This may account for the widespread irresponsibility to take contraceptive precautions. "It is certainly causing much disquiet among consultant gynaecologists, 92 percent of whom (including many with extremely liberal views) are not in favor of abortion on demand."

"If they (legislators) and the public do want abortion on demand they should say so, modify the Act accordingly, and make provisions for its application which do not involve coercion of unwilling gynaecologists or make for encroachment on the beds and other facilities of hospital gynaecological departments to the detriment of the care of women with genuine gynaecological disorders. In this context it should be pointed out that to make abortion on demand legal will not make it ethical."

Among other aspects with which the consultant gynaecologists expressed considerable concern was that hospital admission of patients with gynaecologic disease, such as cancer, was delayed, sometimes for months, "because abortion cases had to be given priority." In addition to the shortage of hospital beds, time for adequate preoperative evaluation of patients for possible therapeutic abortion, which the consultants felt was necessary, resulted in interference with teaching and training programs of junior medical staff and students. Fear that the number and quality of physicians entering the speciality of obstetrics and gynaecology would decline was expressed by sixty percent of the consultants. This report emphasizes the many facets of the therapeutic abortion problem.

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Case Report

Lymphatic Cyst of the Stomach

RONALD ISAACSON, M.D.,* O. THERON CLAGETT, M.D.†
GEORGE M. FARROW, M.D.‡

Benign tumors, though uncommon, can arise from various tissues which make up the stomach wall. About 5% of all neoplasms of the stomach are estimated to be benign. Even rarer are benign lymphatic abnormalities of the stomach. Chodack and Hurwitz[1] in 1964 reported a case of lymphangiectasis of the stomach, and in their review of the world's literature they found only three or possibly four examples of lymphangioma of the stomach, all of which had been reported as incidental findings noted at autopsy. In the case reported by Chodack and Hurwitz, the patient proved to have a lymphangiectatic lesion that presented as a polypoid tumor of the stomach. They found only one other reported example of a lesion similar to theirs. A lymphangiectatic lesion may logically be considered a variant of lymphangioma. In 1965 Ochsner and Janetos[2] reported the case of one patient with lymphangioma of the stomach in a series of 80 patients with benign gastric tumors.

We wish to report a case in which x-ray examination demonstrated a gastric tumor which proved at operation to be a lymphatic cyst. Insofar as we can determine from a review of the literature, no similar lesion has been reported previously.

Report of a Case

A 79-year-old white man in good general health was seen at the Mayo Clinic on April 29, 1969. He had undergone segmental resection of the sigmoid for a polypoid lesion 12 years previously. The lesion, a low-grade adenocarcinoma, had invaded its pedicle. The regional lymph nodes were negative for metastasis. The patient had returned annually for follow-up examinations and had had no evidence of further intestinal problems. X-ray examinations of the upper gastrointestinal tract had been made on several occasions because of symptoms suggesting esophageal hiatal hernia. Further x-ray studies were carried out because the patient complained of vague postprandial gastric distress. A mass was evident in the wall of the lesser curvature of the stomach, just proximal to the pylorus. Ulceration of gastric mucosa was not apparent. The lesion appeared to be intramural in location and had a sharp border (Figure 1). Fortunately, roentgenograms of the stomach made in September 1964 were available for review and comparison. Though no lesion was apparent at that time one may have been present in minute form.

Physical examination showed essentially normal findings for a patient of 79 years of age, as did all laboratory studies. Only roentgenograms of the stomach showed evidence of abnormality.

Clinically, the lesion of the stomach was suspected to be a gastric leiomyoma or lipoma rather than a malignant lesion. Operation was performed on May 6, 1969; the abdomen was explored through an upper midline incision. A cystlike lesion about 5 cm in diameter was present in the wall of the lesser curvature. Mucosal ulceration was not evident. Enucleation was attempted, but the cystic lesion was so thin-walled and the gastric mucosa so adherent that the cyst ruptured and a clear lymphlike fluid escaped. The surrounding tissue was excised and the gastric defect repaired.

Pathologically the cyst, 3.5 cm in diameter (collapsed),



Fig. 1—Upper gastrointestinal series demonstrating an intramural mass in lesser curvature of stomach.

*Mayo Graduate School of Medicine (University of Minnesota), Rochester: Resident in Surgery.
†Mayo Clinic and Mayo Foundation: Department of Surgery.
‡Mayo Clinic and Mayo Foundation: Department of Surgical Pathology.

was situated beneath the muscularis mucosae intramurally in the gastric wall. It was unilocular, was lined with flattened endothelial cells, and contained a small amount of clear lymph. The overlying mucosa demonstrated mild chronic gastritis. A diagnosis of intramural lymphatic cyst was made (Figure 2).

The postoperative course was uneventful and the patient was dismissed from the hospital on the fifth postoperative day.

Comment

Cystic lesions of the stomach are rarely reported. Eliason and Wright[3] stated that about 5% of the benign tumors of the stomach are cysts. None of the lesions they reported were considered to be lymphatic cysts.

In our patient the lesion presented as a filling defect in the wall of the lesser curvature of the stomach, producing few, if any, symptoms. But in retrospect it may have been evident on roentgenograms made five years previously, since which time it had increased in size. The surgeon did not think that it would prove to be malignant, but its increasing size and the possibility of gastric ulceration developing in this region led to the recommendation for surgery.

Other benign tumors of the stomach, such as leiomyoma, lipoma, and adenoma are more common than lymphatic lesions. This example of a lymphatic cyst, however, makes it necessary to add this lesion to the list of benign tumors of the stomach.

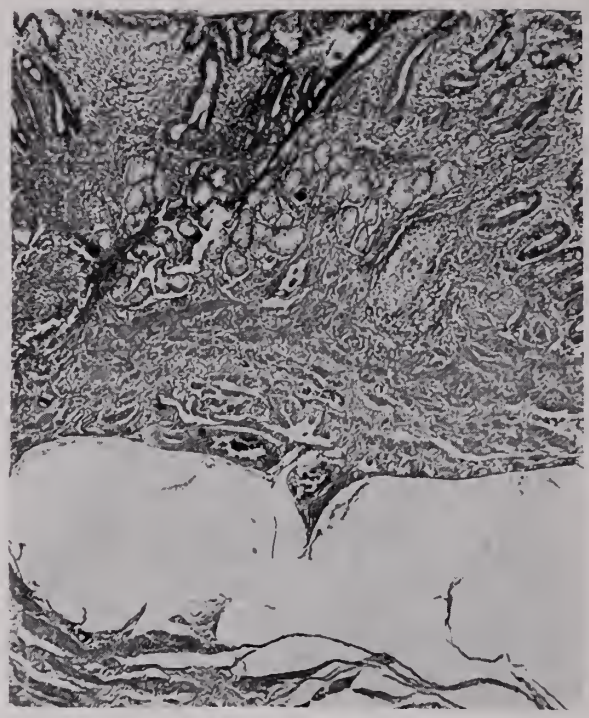


Fig. 2—Intramural gastric lymphatic cyst (collapsed). (Hematoxylin and eosin; ×40.)

Conclusion

Benign tumors of the stomach are uncommon; benign cystic lesions of the stomach are even rarer. Lymphatic cysts of the stomach, of the type reported, appear to be the rarest of all benign gastric lesions.

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1. Chodack, P., and Hurwitz, A.: Lymphangiectasis of Stomach Simulating Polypoid Neoplasm. Arch Intern Med (Chicago) 113:225, 1964.
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3. Eliason, E. L., and Wright, V. W. M.: Benign Tumors of the Stomach. Surg Gynec Obstet 41:461, 1925.

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*Dr. George Crane: The Quotable Dr. Crane, 1968.

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(Continued from page 1188)

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*Slanger, A.: Med. Times *94*:150 (Feb.) 1966.

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In 1962, Roche Laboratories introduced Fluorouracil Roche® (5-fluorouracil). Early clinical work with this drug suggested that it possessed a selective cytotoxic activity when applied topically to certain kinds of lesions. Based on this work and years of clinical trials, a standardized form of topical fluorouracil can now be recommended for treatment of multiple solar or actinic keratoses.

Efudex®(fluorouracil)—a new alternative to conventional therapy

Efudex presents the physician with a topical alternative to surgery in the treatment of solar or actinic keratoses. It is effective, comparatively inexpensive and especially well-suited for treatment of multiple lesions. Important, too, is the highly desirable cosmetic result. Clinical experience demonstrates that treatment with Efudex results in an extremely low incidence of scarring.*

Highly effective on first and later applications

In clinical trials, depending on the dosage form and strength used, complete involution occurred in 77 to 88 per cent of lesions following treatment. The rate of recurrence was low, ranging from 1.7 to 5.6 per cent up to a year after completion of therapy. When lesions did recur or new ones appeared, repeated courses of Efudex therapy proved effective.*

'2/68—After 11 days of treatment. ·ythema is seen at site of keratoses. In ldition, numerous lesions not apparent ·ior to therapy have become manifest y sharply defined reactions. Intervening ·in, also treated, shows no response to ıerapy.

/19/69—One year after cessation of ıerapy. Skin appears clear with no evi- ence of scarring. Examination reveals ıck of recurrence or the formation of ew lesions.



Predictable sequence of therapeutic response

Two to four weeks constitutes a typical course of Efudex therapy. The response is usually characteristic and predictable. After three or four days of treatment, erythema begins to appear in the area of the keratoses. This is followed by an intense inflammatory response, scaling and occasionally moderate tenderness or pain. The height of the inflammatory reaction generally occurs two weeks after the start of therapy, and then begins to subside as treatment is stopped. Within two weeks of discontinuing medication, the inflammation is usually gone. A mild erythema may remain for two to three months before gradually receding.

Selective—with a high degree of safety

Despite the temporary unsightliness and discomfort of the inflammatory episode, Efudex is, in general, more readily tolerated than surgery. Clinical work shows the intense inflammatory response to be limited to the area of the lesion. Normal skin is not similarly affected. Another measure of Efudex safety: systemic absorption of topical fluorouracil was insignificant, indicating a low risk of systemic toxicity.*

Two strengths—two convenient dosage forms

Efudex is available as a 2% or 5% solution or as a 5% cream. It is applied twice daily by the patient with a nonmetal applicator or suitable glove.

Before prescribing Efudex, however, there are two important considerations. First, please consult the complete prescribing information for precautions, warnings and adverse reactions. Second, advise the patient that treated lesions should respond with the characteristic but transient inflammation. A positive sign that Efudex is working for them.

*Data on file, Hoffmann-La Roche Inc., Nutley, New Jersey.

2% and 5% Solutions; 5% Cream Applied twice daily—resolves solar or actinic keratoses.

new Efudex® (fluorouracil) cream/solution



For full prescribing information, please see the following page.

Roche introduces

Efudex®

(fluorouracil) cream/solution the new standardized topical for solar/actinic keratoses

Description: Efudex solutions and cream are topical preparations containing the fluorinated pyrimidine 5-fluorouracil, an antineoplastic antimetabolite.

Efudex Solution consists of 2% or 5% fluorouracil on a weight/weight basis, compounded with propylene glycol, tris-(hydroxymethyl) aminomethane, hydroxypropyl cellulose, parabens (methyl and propyl) and disodium edetate.

Efudex Cream contains 5% fluorouracil in a vanishing cream base consisting of white petrolatum, stearyl alcohol, propylene glycol, polysorbate 60 and parabens (methyl and propyl).

Actions: There is evidence that the metabolism of fluorouracil in the anabolic pathway blocks the methylation reaction of deoxyuridylic acid to thymidylic acid. In this fashion fluorouracil interferes with the synthesis of deoxyribonucleic acid (DNA) and to a lesser extent inhibits the formation of ribonucleic acid (RNA). Since DNA and RNA are essential for cell division and growth, the effect of fluorouracil may be to create a thymine deficiency which provokes unbalanced growth and death of the cell. The effects of DNA and RNA deprivation are most marked on those cells which grow more rapidly and which take up fluorouracil at a more rapid pace. The catabolic metabolism of fluorouracil results in degradative products (*e.g.*, CO_2, urea, α-fluoro-β-alanine) which are inactive.

Studies in man with topical application of ^{14}C-labeled Efudex demonstrated insignificant absorption as measured by ^{14}C content of plasma, urine and respiratory CO_2.

Indications: Efudex is recommended for the topical treatment of multiple actinic or solar keratoses.

Contraindications: Efudex is contraindicated in patients with known hypersensitivity to any of its components.

Warnings: If an occlusive dressing is used, there may be an increase in the incidence of inflammatory reactions in the adjacent normal skin.

Prolonged exposure to ultraviolet rays should be avoided while under treatment with Efudex because the intensity of the reaction may be increased.

Usage in Pregnancy: Safety for use in pregnancy has not been established.

Precautions: If Efudex is applied with the fingers, the hands should be washed immediately afterward. Efudex should be applied with care near the eyes, nose and mouth. To rule out the presence of a frank neoplasm, a biopsy should be made of those areas failing to respond to treatment or recurring after treatment.

Adverse Reactions: The most frequently encountered local reactions were pain, pruritus, hyperpigmentation and burning the site of application. Other local reactions included dermatit scarring, soreness and tenderness.

Also reported were insomnia, stomatitis, suppuration, scalin swelling, irritability, medicinal taste, photosensitivity and lacrimation.

Laboratory abnormalities reported were leukocytosis, thrombocytopenia, toxic granulation and eosinophilia.

Dosage and Administration: Efudex should be applied twice da with a nonmetal applicator or suitable glove in an amount of tl solution or cream sufficient to cover the lesion. When Efudex i applied to a lesion, a response occurs with the following sequei erythema, usually followed by vesiculation, erosion, ulceration necrosis and epithelization. The lower frequency and intensity activity in adjacent normal skin indicate a selective cytotoxic property. Medication should be continued until the inflammator reaction reaches the erosion, necrosis and ulceration stage, at which time use of the drug should be terminated. The usual duration of therapy is from 2 to 4 weeks. Complete healing of th lesion may not be evident for 1 to 2 months following cessation Efudex therapy.

How Supplied: Efudex Solution, 10-ml drop dispensers—contain 2% or 5% fluorouracil on a weight/weight basis, compounded with propylene glycol, tris(hydroxymethyl)aminomethane, hydroxypropyl cellulose, parabens (methyl and propyl) and disodium edetate.

Efudex Cream, 25-Gm tubes—containing 5% fluorouracil in vanishing cream base consisting of white petrolatum, stearyl alcohol, propylene glycol, polysorbate 60 and parabens (methy and propyl).

Clinical Studies: The effectiveness of the three preparations as determined by complete involution of solar keratoses was: 2% Solution, 77% of 282 lesions; 5% Solution, 88% of 202 lesions; and 5% Cream, 85% of 189 lesions. In those lesions whe complete involution followed treatment, the rate of possible recurrences observed clinically at periods up to 12 months or mo was: 2% Solution, 4.6% of 218 lesions; 5% Solution, 1.7% of 17 lesions; and 5% Cream, 5.6% of 160 lesions. Because of the toxic potential of fluorouracil, some physicians preferred to use the 2% solution when large areas were to be treated. Approximately 30% of the lesions required treatment for two weeks or less; approximately 78% required four weeks or less for adequate treatment.

ROCHE Roche LABORATORIES
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

Laboratory Letter

Experience with Atypical or Positive Cytology Smears

From January 1958 to July 1969, we reported 1,604 atypical or positive smears representing 1,169 patients (Group II, III, IV, or V) among 137,857 cases. Of these patients, 633 had cervical cones with 282 carcinomas in situ and 90 invasive carcinomas being reported. The remaining cervical cones showed benign to severe dysplasia. Also, as you can see in the following Table, 16 endometrial carcinomas were detected.

Group		Number of Cases	One Smear	Repeat Smear: Positive	Repeat Smear: Negative	Conizations: Benign	Conizations: C.I.S.	Conizations: Invasive	Endometrial Carcinoma	Lost
Benign Atypia	II*	62	3	32	27	20	1	1	0	3
Suspicious	III	798	210	258	321	172	145	31	8	129
Prob. malig.	IV	278	162	89	27	68	115	41	6	33
Malignant	V	31	31	0	0	1	11	17	2	2
Total		1169	415	379	375	261	282	90	16	167

*The Benign Atypia, Group II, category may be a little misleading. It includes only those Group II cases that went on to have Group III or worse smears. In our experience, less than 3 percent of those initially grouped as II go on to have suspicious or malignant smears.

The 167 lost cases listed in our totals of positive smears represent cases in which we were unable to obtain follow-up reports from physicians on subsequent smears or treatment.

Our study indicates that about one half Group III cases had conizations of which one half were malignant. The half that did not have a cone had negative repeat smears and have remained negative.

Group IV smears led to conization in 80 percent. Of these 224 cones, about 70 percent were malignant; 10 percent had negative repeat smears.

Although only 31 had been grouped as V (malignant cells present), 30 of these proved to be malignant.

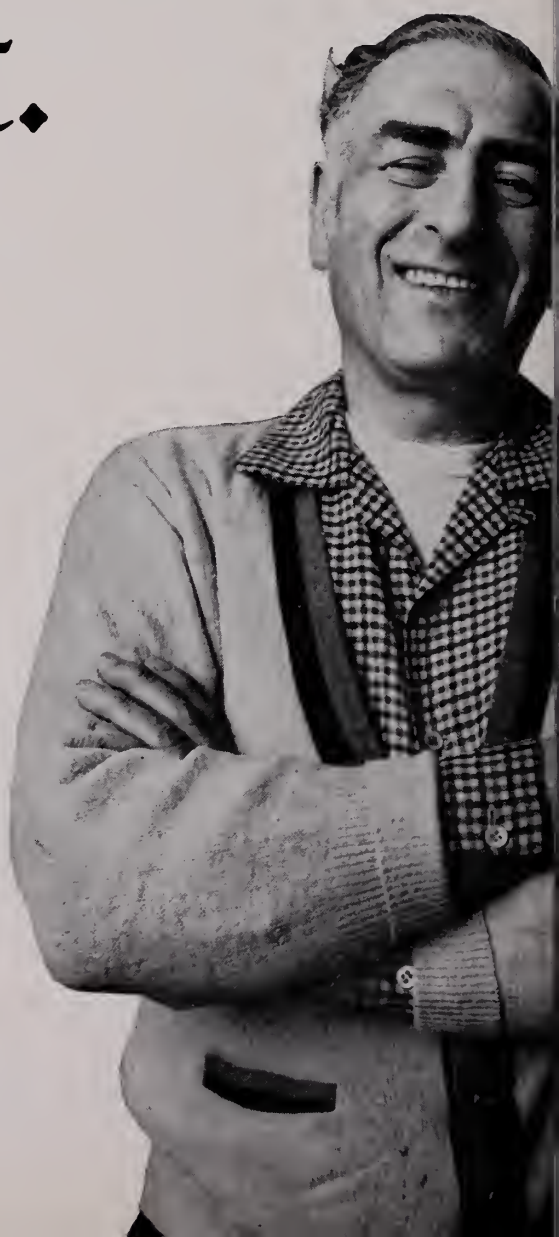
A particularly interesting group of patients are those with a diagnosis of dysplasia on cervical conization. The distinction between dysplasia and carcinoma in situ is often a narrow one. In time, some cases of dysplasia may evolve into in-situ lesions. We have had 56 cases diagnosed as dysplasia, and three of these had follow-up cones that showed carcinoma in situ. The remaining cases of dysplasia had negative follow-up smears, less abnormal than before, or had repeat non-malignant cones.

Follow-up smears after cones show that hysterectomy has been curative in in-situ carcinomas. Four cases had recurrent positive smears, and biopsies showed carcinoma in situ of the vagina. Five cases that showed in-situ changes on cervical cones did not have hysterectomies. These have been followed for up to ten years, and smears have remained negative. All of these have been in young women who desired more children. An unknown number of patients after cervical cones had positive smears and/or biopsies, and hysterectomy was then done. None of these cases diagnosed as in-situ carcinoma are known to have progressed to invasive tumors, though in several cases localized invasion was found in the hysterectomy specimen after carcinoma in situ was diagnosed in the cone.

Wayne A. Chadbourn, M.D.
Minneapolis, Minnesota

Acknowledgment: I should like to thank our three excellent cytotechnologists: Mrs. Laurie Harris, Mrs. Pat Christensen, and Miss Mary Lea, for collecting the data used in this Letter.

Menrium® treats the menopausal symptoms that bother him most.



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His wife has a lot of different menopausal symptoms, but only a few really irritate *him*. Her hot flashes, her vertigo, her palpitations—that's *her* problem. What really bothers him is her nervousness, her irritability and her excessive anxiety, often expressed by endless "book-shuffling, chain-smoking, reading-lamp" insomnia!

Menrium takes care of hot flashes, vertigo, palpitations in most menopausal women. Menrium provides the well-known antianxiety action of chlordiazepoxide (Librium®) and water-soluble esterified estrogens. It therefore relieves more symptoms than either component separately. It takes care of the vasomotor symptoms as well as the emotional symptoms. This means the symptoms that bother his wife most. And the symptoms that irritate him most.

So, to help them both get through *her* menopause, remember Menrium.



Before prescribing, please consult complete product information, a summary of which follows:

Indications: Management of manifestations generally associated with the menopausal syndrome—anxiety and tension, vasomotor complaints and hormonal deficiency states.

Contraindications: Women with cancer of breast or genitalia, except inoperable cases, and those with known hypersensitivity to chlordiazepoxide and/or esterified estrogens.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Exclude other possible causes of menopausal syndrome manifestations, such as pregnancy. Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions) similar to those seen with barbiturates have been reported following discontinuance of chlordiazepoxide HCl. Potential benefits of use in pregnancy, lactation or women of childbearing age should be weighed against possible hazards to mother and child. Clinical data inadequate on safety in pregnancy.

Precautions: In elderly and debilitated patients, limit dosage to smallest effective amount of chlordiazepoxide (initially 10 mg or less per day) to preclude ataxia or oversedation; increase gradually as needed and tolerated. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects—particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in patients with impaired renal or hepatic function. Paradoxical reactions to chlordiazepoxide (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients. Employ usual precautions in the treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation very rarely reported in patients receiving Librium® (chlordiazepoxide) and oral anticoagulants.

Adverse Reactions: Untoward effects seen with either compound alone may occur with Menrium. With chlordiazepoxide, drowsiness, ataxia and confusion reported in some patients, particularly in the elderly and debilitated; while usually avoided by proper dosage adjustment, these are occasionally observed at lower dosage ranges. Also reported have been a few instances of syncope; isolated occurrences of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido, and occasional reports of blood dyscrasias, including agranulocytosis, jaundice and hepatic dysfunction. Periodic blood counts and liver function tests advisable during protracted treatment. Changes in EEG patterns (low-voltage fast activity) observed during and after chlordiazepoxide treatment.

With estrogens, headache, nausea and vomiting, anorexia, gastrointestinal discomfort, dysuria and urinary frequency, jitteriness, breast engorgement, formation of breast cysts, skin rashes and pruritus occasionally seen. Administration may also be associated with uterine bleeding and/or followed by withdrawal bleeding.

Usual Dosage: One tablet t.i.d. for 21 days, followed by one-week rest periods.

Menrium® T.I.D.

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5 mg chlordiazepoxide	5-4	0.4 mg water-soluble esterified estrogens
10 mg chlordiazepoxide	10-4	0.4 mg water-soluble esterified estrogens

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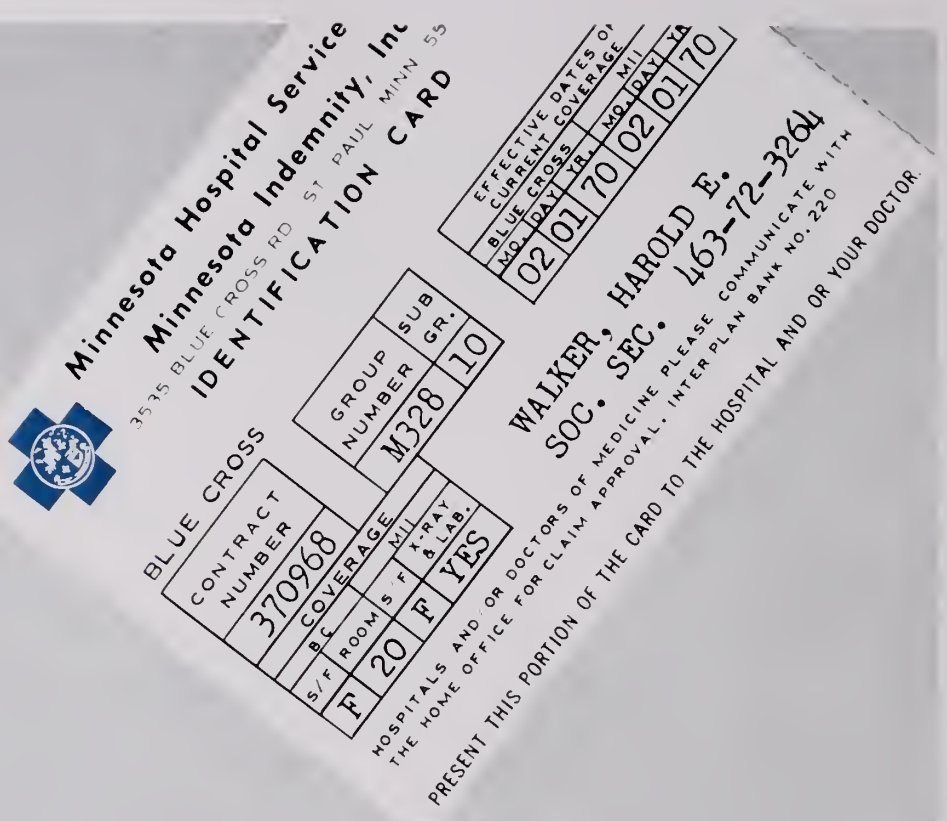
The Hennepin County Academy of General Practice Annual Invitational Banquet, Monday evening, November 23, 1970, at the Radisson Hotel Downtown. Social hour will begin at 6:00 p.m. with dinner scheduled for 7:30 p.m. The speaker will be Mr. Robert Manry, and his speech topic is "Tinkerbelle's Run to Glory." We invite, and encourage to attend, all physicians and their guests both from the metropolitan and out-of-state areas. Contact Donald L. Wright, M.D., 3620 Central Avenue N.E., Minneapolis, Minnesota 55418, telephone 780-1151, area code 612.

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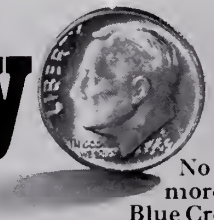
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Literature on indications and dosage available on request.

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References:
(1) Siver, R. H.: CMD, 21:109, September 1954. (2) Frykman, H. H.: Minn. Med., 38:19-27, January 1955. (3) McGivney, J.: Tex. State Jour. Med., 51:16-18, January 1955. (4) Quehl, T. M.: Jour. of Florida Acad. Gen. Prac., 15:15-16, October 1965. (5) Weekes, D. J.: NY State Jour. Med., 58:2672-2673, August 1958. (6) Ellis, S. and Spratt, J. S.: JOUR. AMER. GER. SOC., 18:410-415, May 1970.



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Effectiveness: Because its antibacterial component is DECLOMYCIN ® Demethylchlortetracycline, DECLOSTATIN should be equally or more effective therapeutically than other tetracyclines in infections caused by tetracycline-sensitive organisms. The antifungal component, nystatin, protects against superinfection by antibiotic-resistant fungal overgrowth (particularly monilia) in the intestinal tract.

Contraindication: History of hypersensitivity to demethylchlortetracycline or nystatin.

Warning: In renal impairment, usual doses may lead to excessive accumulation and liver toxicity. Under such conditions, lower than usual doses are indicated and, if therapy is prolonged, serum level determinations may be advisable. A photodynamic reaction to natural or artificial sunlight has been observed. Small amounts of drug and short exposure may produce an exaggerated sunburn reaction which may range from erythema to severe skin manifestations. In a smaller proportion, photoallergic reactions have been reported. Patients should avoid direct exposure to sunlight and discontinue drug at the first evidence of skin discomfort. Necessary subsequent courses of treatment with tetracyclines should be carefully observed.

Precautions: Overgrowth of nonsusceptible organisms may occur. Constant observation is essential. If new infections appear, appropriate measures should be taken. In infants, increased intracranial pressure with bulging fontanels has been observed. All signs and symptoms have disappeared rapidly upon cessation of treatment.

Side Effects: Gastrointestinal system—anorexia, nausea, vomiting, diarrhea, stomatitis, glossitis, enterocolitis, pruritus ani. Skin—maculopapular and erythematous rashes; a rare case of exfoliative dermatitis has been reported. Photosensitivity; onycholysis and discoloration of the nails (rare). Kidney—rise in BUN, apparently dose-related. Transient, reversible, nephrogenic diabetes insipidus with excessive thirst and polyuria (rare). Hypersensitivity reactions—urticaria, angioneurotic edema, anaphylaxis. Teeth—dental staining (yellow-brown) in children of mothers given this drug during the latter half of pregnancy, and in children given the drug during the neonatal period, infancy and early childhood. Enamel hypoplasia has been seen in a few children. If adverse reaction or idiosyncrasy occurs, discontinue medication and institute appropriate therapy. Demethylchlortetracycline may form a stable calcium complex in any bone-forming tissue with no serious harmful effects reported thus far in humans.

Average Adult Daily Dosage: One tablet b.i.d. Should be given 1 hour before or 2 hours after meals, since absorption is impaired by the concomitant administration of high calcium content drugs, foods and some dairy products. Treatment of streptococcal infections should continue for 10 days, even though symptoms have subsided.

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President's Letter

Group Practice

THERE ARE many who say that group practice, meaning the prepaid, closed-panel variety, is the only answer to the problems engendered by our health-care delivery system. This type of practice is damned by others as a threat to our freedom in the choice of physician. Two of our most widely circulated lay magazines published feature articles, one entitled "Don't Get Sick in America" and the other, "Our Ailing Medical System." The authors of these feature stories proceeded to make the claim in a very derogatory manner that since currently there is a "non-system" in the provision of health care, any change in contemporary practices would be an improvement, and that much of the great tradition of altruism and selflessness historically ascribed to medicine is so much "hogwash." To denigrate physicians seems to be a profitable headline-producing endeavor.

One of the pioneers in prepaid group practice, Sidney R. Garfield, a director of the Kaiser Foundation Health Plan and Hospitals, states that the Kaiser-Permanente program alters the traditional health-care delivery system in only two ways. First, it substitutes prepayment for the fee for service, and second, it organizes the many units of medical-care resources into a coordinated practice in integrated clinics and hospitals. He continued by reporting that elimination of the fee was always a must in the concept of the Kaiser plan, because the interposition of the fee was considered to be a barrier to early entry of a sick person to medical care. On the other hand, when the fee for medical services was abolished entirely, the result was an uncontrolled flood of well, worried well, early sick and sick people overloading the system and vitiating the physician's time.

It is my considered opinion that there is no single easy answer to the problem. Different systems of care may be necessary for different population and geographic groups. Despite the allegations of writers who like to sell catchpenny tracts to the public prints, most physicians welcome innovations and recognize that group practice is the best answer to health care in needy areas. Dr. Irvine H. Page has summarized my attitude in his statement that "most medical practice is concerned with fear, pain, loneliness, and uncertainty, treatable only in part by medical economics, by planning by those remote from medicine, or by massive government subsidy; but mainly by wisdom touched with sympathy."

R. J. Jackman

Raymond J. Jackman, M.D., President,
Minnesota State Medical Association

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Serum Thyroxine

M. DESMOND BURKE, M.D.*

THE PROTEIN BOUND iodine determination remains the most widely used laboratory test of thyroid function, and in most cases it provides an accurate assessment of thyroid status. There are, however, two extra-thyroidal factors which invalidate the protein bound iodine: iodine contamination of serum and variations in thyroid binding protein. The iodine contaminants of x-ray contrast media and the elevation of thyroid binding protein by estrogen contained in oral contraceptive agents are important sources of false protein bound iodine values.

Although there is not, as yet, a simple specific method for the measurement of metabolically active free thyroid hormone in the serum, there are a variety of reliable newer techniques which, if chosen properly, will eliminate the above difficulties with the protein bound iodine determination.

Two relatively simple modifications of the protein bound iodine method will eliminate many of the sources of iodine contamination; these modifications are utilized in the butanol extractable iodine and thyroxine by column methods.[1] Furthermore, the newer "competitive protein binding assay"[2,3,4] methods for the measurement of total serum thyroxine are entirely independent of iodine contamination.

Greater difficulties are encountered in combating the inaccuracy of the protein bound iodine in the presence of variation in thyroid binding capacity. Recently developed techniques for the direct[5,6,7] and indirect[3,8] measurement of the "free" (non-protein bound) thyroxine, however, are promising in this regard.

Protein Bound Iodine Methods

Methods for the determination of the protein bound iodine are dependent upon the ability of iodine to catalyze the reduction of the ceric ion by arsenious acid. The reaction is accompanied by a color change which is amenable to colorometric analysis. Automated protein bound iodine determinations using the "autoanalyzer" are in common use. The use of acid digestion in some protein bound iodine methods causes false low protein bound iodine values in the presence of mercuric ions. As a consequence, mercurial diuretic therapy is an important cause of decreased protein bound iodine values in many of the methods in current use. Small amounts of inorganic iodides which circulate in serum unbound to serum protein are not measured in the protein bound iodine method. Excessive amounts of inorganic iodide, capable of interference, may be present in the serum following the ingestion or topical application of a variety of therapeutic agents. The use of potassium iodide expectorants and the application of topical iodides to the skin are examples of iodine contaminants which can falsely elevate protein bound iodine values. In general, inorganic iodides are rapidly eliminated from the circulation following cessation of therapy, and the protein bound iodine inaccuracies are short-lived.

The organic iodine present in x-ray contrast media remains bound to serum protein for varying lengths of time, resulting, consequently, in a more troublesome source of error. Compounds such as Hypaque which are used in intravenous pyelography are generally eliminated from the circulation in a matter of weeks; whereas bronchographic compounds such as Lipiodol or myelographic compounds such as Pantopaque may remain for months or years as a continuing source of falsely elevated protein bound iodine determinations.[9]

Butanol-Extractable Iodine

Butanol extraction of serum, followed by idoine determination of the serum extract, represents a refinement of the protein bound

*Associate Pathologist, Mount Sinai Hospital, Minneapolis.

iodine that removes many of the sources of iodine contamination. All inorganic iodides, and many of the organic iodides of the various x-ray contrast media, are not extracted into butanol; thus, they are not included in the butanol extractable iodine determination. Furthermore, the nonhormonal abnormal iodoprotein compounds that are released into the circulation in a variety of pathologic conditions affecting the thyroid gland, notably in chronic thyroiditis, are not measured in the butanol extractable iodine determination although they commonly result in falsely elevated protein bound iodine values.[10]

Thyroxine by Column

Another method of diminishing iodine contamination is through the use of column chromatography of serum prior to the protein bound iodine determination. This technical modification of the protein bound iodine determination, called the thyroxine by column method, is similar in its specificity to the butanol extractable iodine; it excludes inorganic iodides, abnormal iodoproteins, and some of the radiographic compounds. It has replaced, for practical purposes, the more cumbersome butanol extractable iodine method. An additional advantage over the butanol extractable iodine is that the pattern of elution from the chromatographic column indicates the presence of gross iodine contamination, prior to the definitive protein bound iodine determination.[1]

Both of these techniques are useful in the various clinical conditions associated with the presence of abnormal iodoproteins in serum and, when used in conjunction with the protein bound iodine, are capable of providing a rough estimate of the level of these non-hormonal compounds. Normal values for both the butanol extractable iodine and thyroxine by column methods are usually approximately 2 μgm lower than the corresponding protein bound iodine values. Wider than normal differences between the protein bound iodine and either the butanol extractable iodine or the thyroxine by column values, indicating the presence of abnormal iodoproteins, have been reported in chronic thyroiditis, subacute thyroiditis, following I^{131} therapy, in certain forms of congenital goiter, and in thyroid adenomas.[10] Undoubtedly both methods measure serum thyroxine more accurately than does the protein bound iodine; their precision, however, is less. Furthermore, in the presence of variation in thyroid binding protein, neither of the above tests offers any advantage over the routine protein bound iodine determination.

Total Serum Thyroxine by "Competitive Protein Binding Assay"

A variety of methods using the principles of "competitive protein binding assay" have been devised for the determination of total serum thyroxine.[2,3,4] Unlike the techniques already discussed, these methods do not measure iodine; thus they are unaffected by either endogenous or exogenous iodine contamination. In the "competitive protein binding assay" technique, small amounts of radioactively labeled thyroxine are equilibrated with pooled serum. In such a system most of the radioactive thyroxine binds to the thyroid binding protein of the serum pool, and a minute amount remains free. The ratio of bound to free radioactive thyroxine reflects the proportion of bound and free thyroxine in the serum pool. The addition of standard amounts of thyroxine to the serum pool alter the free to bound radioactive thyroxine ratio. Thus, the construction of a standard curve, from which the total thyroxine concentration of unknown sera may be determined, is possible.

Separation of free and bound thyroxine is effected by a variety of techniques, including the use of anion exchange resins and sephadex gel filtration. Recent reports of essentially 100% recovery of added thyroxine[3,4] and studies demonstrating a lack of interference by the in vitro addition of a variety of drugs including iodine compounds would seem to attest to the specificity of these techniques.[2,3,4] The only materials

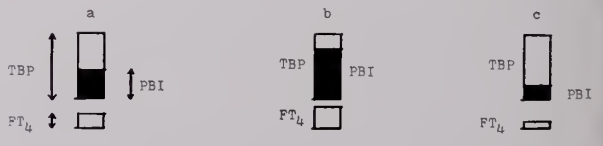


Fig. 1—Relationship between free and bound thyroxine (T_4). (a) Normal euthyroid. (b) Hyperthyroidism: increased saturation of thyroid binding protein (TBP); increased free thyroxine (FT_4). (c) Hypothyroidism: decreased saturation of thyroid binding protein; decreased free thyroxine.

considered to interfere with competitive binding techniques, other than analogs of thyroxine and tri-iodothyronine, are phenylbutazone and dilantin. Elevation of serum thyroxine, following the in vitro addition of both of those compounds to serum, is presumably based upon their ability to displace thyroxine from thyroid binding protein.[4]

Free Thyroxine

Variations in thyroid binding protein provide the second major source of error in the protein bound iodine determinations. Most of the circulating thyroxine is bound to thyroid binding proteins. The minute portion that is free or unbound is considered to represent the metabolically active fraction.[11] In the euthyroid state the thyroid binding proteins are not completely saturated with thyroxine (Figure 1 a). In the hyperthyroid state there is an increase in total thyroxine that is reflected in an increased saturation of thyroid binding protein, and an increased concentration of the free thyroxine (Figure 1 b). In hypothyroidism there is a decrease in free thyroxine and a decreased saturation of thyroid binding protein (Figure 1 c). In both instances, measurement of the protein bound thyroxine, as determined by the protein bound iodine, the thyroxine by column, or the total serum thyroxine methods, is proportional to the free thyroxine concentration.

In the presence of primary variation in thyroid binding protein, the protein bound iodine is no longer proportional to the free thyroxine, and consequently is not a true index of thyroid status. No change occurs in the free thyroxine with primary changes in thyroid binding protein: the changes which occur in the protein bound iodine vary directly with the changes occurring in the thyroid binding proteins. (Figures 2 a, b, c).

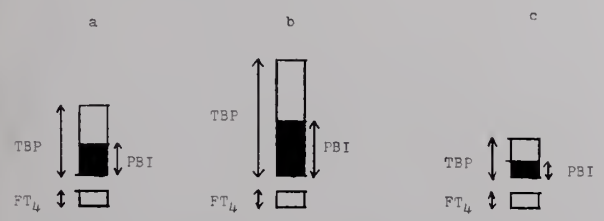


Fig. 2—Primary variation in thyroid binding protein (TBP). Diagrammatic representation of relationship between free and bound thyroxine (T_4). (a) Normal euthyroid. (b) Primary increase in thyroid binding protein with increase in protein bound iodine (PBI) and normal free thyroxine (FT_4). (c) Primary decrease in thyroid binding protein with decrease in protein bound iodine and normal free thyroxine.

Thus, the protein bound iodine, or any measurement of protein bound thyroxine, will be invalid in any of the clinical conditions outlined in the Table. The false elevation of the protein bound iodine occurring during pregnancy and accompanying the use of oral anti-ovulatory agents seriously limits its usefulness; a direct or indirect assessment of free thyroxine is necessary under such circumstances.

TABLE
Causes of Variations in Thyroid Binding Protein Capacity (TBP)

Increased TBP	Decreased TBP
Estrogen therapy (oral anti-ovulatory agents)	Androgen therapy
Pregnancy	Nephrosis
Primary, genetic	Advanced cirrhosis
Acute intermittent porphyria	Primary, genetic
Perphenazine therapy	Diphenylhydantoin (Dilantin)
Acute liver disease	Salicylates
Hypothyroidism	Hyperthyroidism
	"Sick euthyroid" patients

Recently, methods for the determination of free thyroxine have been described and are currently available.[5,6,7] All of the reported methods are essentially similar in principle, involving the initial addition of tracer amounts of radioactive iodine to serum, followed by separation of the bound and free thyroxine by either dialysis or ultrafiltration. Estimation of the radioactivity in the free and bound portions provides an estimation of the percentage of free thyroxine; the product of the percentage of free thyroxine and the protein bound iodine value represents the free thyroxine concentration.

The reported normal values for free thyroxine vary somewhat, depending upon the method used, but they yield similar relative changes in a variety of pathologic and physiologic settings.[12] In general, the free thyroxine determination is a good index of thyroid status; however, varying numbers of acutely and severely ill euthyroid patients exhibit free thyroxine levels that are significantly higher than those of normal euthyroid patients.[13,14] In this regard, it has been suggested that the serum free thyroxine level may be a more indirect parameter of true thyroid status than had hitherto been realized. It has, furthermore,

been proposed that the cellular thyroxine content may more closely reflect thyroxine activity than does the free thyroxine value.[12]

Resin Uptake of I^{131} T_3 (RT_3), "T_3 Test"

The resin uptake of radioactive T_3 (T_3 test) provides an indirect estimate of the thyroid binding protein levels; it is useful, therefore, in those conditions associated with thyroid binding protein changes. Since the technique is an in vitro radioactive one, without an iodine measurement, it is also useful in the presence of iodine contamination. Serum is incubated with radioactive T_3, and with an inert substance capable of binding thyroid hormones. In the original T_3 test, red blood cells were used as the binding substance.[15] Recent methods use anion exchange resins.[16] The thyroid binding protein of the test serum and the resin compete for the added T_3. Thus, hyperthyroid states accompanied by increased saturation of thyroid binding protein manifest an increase in the resin uptake of radioactive T_3. Hypothyroidism, on the other hand, with low degrees of saturation of thyroid binding protein, shows low resin uptake values (Figure 3). The resin uptake may be used as a primary test of thyroid function; it is more useful, however, when conjoined with a test such as the protein bound iodine, especially in clinical situations complicated by variations in thyroid binding protein. Primary elevations in thyroid binding protein, with falsely elevated protein bound iodine values, show decreased resin uptake values; primary decreases in thyroid binding protein, on the other hand, show low protein bound iodine values and high resin uptakes (Figure 3).

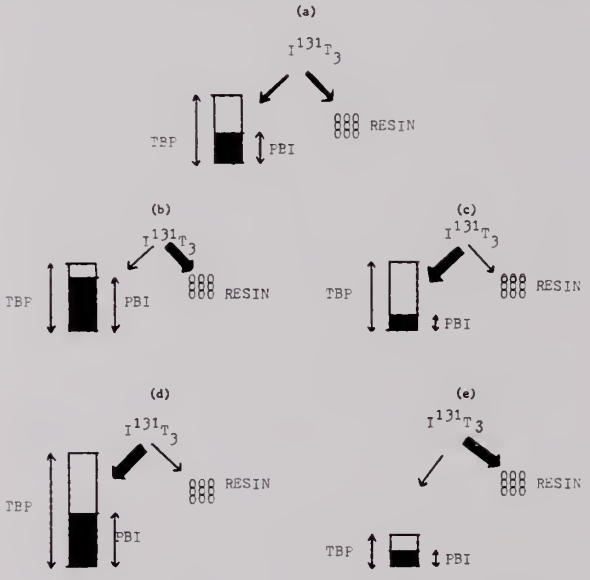


Fig. 3—Diagrammatic representation of the principle of the resin uptake of I^{131} tri-iodothyronine (RT_3) test. The unsaturated portion of the thyroid binding protein (TBP) and the resin compete for labeled tri-iodothyronine (T_3); variations in resin uptake can be seen to be inversely proportional to the amount of unsaturated thyroid binding protein. (a) Euthyroid showing normal RT_3. (b) Hyperthyroidism: decreased unsaturated thyroid binding protein; increased RT_3. (c) Hypothyroidism: increased unsaturated thyroid binding protein; decreased RT_3. (d) Primary increase in thyroid binding protein: absolute increase in unsaturated thyroid binding protein; decreased RT_3. (e) Primary decrease in thyroid binding protein: decrease in absolute amount of unsaturated thyroid binding protein; increase in RT_3.

Free Thyroxine Index

In 1965, Clark and Horn proposed the use of a free thyroxine index calculated from the mathematical product of the protein bound iodine and the resin uptake value.[8] A similar index has recently been advocated by Maclagan and Howorth, derived from the total thyroxine as determined by competitive binding assay and the resin uptake value.[3] The free thyroxine index has been shown to correlate well with thyroid status,[13,17] and to be essentially comparable to direct measurement of free thyroxine.[13,14] In the severely ill euthyroid patient, the free thyroxine index is within the normal range; the free thyroxine in this group of "sick" euthyroid patients may be falsely elevated.[13]

Summary

The protein bound iodine is a useful test of thyroid function in the absence of both iodine contamination and variations in thyroid binding protein.

Contamination due to inorganic iodides and organic non-hormonal iodoproteins is removed following butanol extraction or column chromatography of serum. The latter techniques also remove some, but not all, of the organic iodine compounds used in x-ray diagnosis.

The measurement of serum thyroxine by "competitive protein binding assay" techniques excludes all iodine contamination; it appears to be invalidated only by the presence of thyroxine and tri-iodothyronine analogs, phenylbutazone, diphenylhydantoin (Dilantin) and variations in thyroid binding protein.

Direct measurement of free thyroxine is perhaps the best indicator of thyroid status, except in the case of the severely ill "sick euthyroid" patient, when values indicative of hyperthyroidism are found.

The T_3 test is most useful when used in conjunction with the protein bound iodine, thyroxine by column, or thyroxine assay value in clinical situations complicated by variations in thyroid binding protein.

Both the protein bound iodine and the T_3 test values may be combined to derive a "free thyroxine index," providing an indirect assessment of free thyroxine, which compares favorably with values obtained by direct measurement.

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Experienced Invalid

A man of sixty who had been a grumbler all of his life, had long made a practice of changing his physician at the slightest provocation. One day he called in a young doctor who had gained a considerable reputation.

He was telling the doctor what he thought was the matter with him, when the young M.D. ventured to disagree with him.

"I beg your pardon," said the patient, "it isn't for a young man like you to disagree with an old, experienced invalid like me!"*

*Braude's Speaker's Encyclopedia.

Endocrine Regulation of Reproduction

It has been well known for several years that the events associated with reproduction are regulated by a complicated endocrine system. This system involves interactions between the brain, the pituitary gland, and the gonads. The pituitary gland secretes hormones (particularly LH, FSH and prolactin) which control development and function of the gonads. The gonads respond to this stimulation by secreting sex steroids which act throughout the body to cause the development of secondary sex features and the initiation of events associated with reproduction, including breast development, menstruation, ovulation, onset of puberty, facial hair growth and sperm formation. In addition, the sex steroids feed back upon the brain and the pituitary gland to regulate their functions in a fashion similar to the action of a thermostat. It has been generally accepted that a detailed understanding of these complicated interrelationships might provide insight into mechanisms which can be interrupted to provide a means for safely regulating fertility. Recently, a number of new techniques have become available which involve the use of hormone-specific antibodies.

Studies in our laboratory have involved the development and application of a number of these new techniques for studying the mechanisms which regulate the hormonal events associated with reproduction.

With these methods, it has been possible to continuously monitor the changing hormone concentrations in blood which is removed by means of a cannula. In addition to the development and use of these methods, efforts have been made to utilize hormone-specific, labeled-antibodies to localize the respective hormones in their cells of origin and in target tissues. With radioimmunoassay, biologic, biochemical and morphologic techniques in combination, it has been possible to analyze the endocrine regulation of the events associated with the female reproductive cycle, puberty, pregnancy and menopause.

These studies have revealed the presence of a rather similar hormonal profile throughout the female reproductive cycle in a number of species. The major event in all species studied appears to be the release from the pituitary gland of a single large surge of LH which is followed several hours later by ovulation. Removal of the gonads by castration, and thereby removal of the presumed inhibitory feedback system, results in a fairly prompt increase in circulating levels of LH and FSH, while administration of the sex steroids produced by the gonads results in a prompt decrease in LH and FSH concentrations. The individual components of the oral contraceptives have variable effects depending on dose and duration of administration. However, in general, they act like the endogenous ovarian sex steroids. Low doses sometimes cause the release of LH, while higher doses generally suppress baseline levels of LH and FSH and prevent the normal surge of LH at mid-cycle. Puberty has been found to be associated with an increase in LH and FSH concentrations and the menopausal state is associated with responses similar to those found following castration.

The implication from this study seems to be that determination of blood levels alone may be of little significance unless the physiologic states of the target tissues are known.

A. Rees Midgley, Jr., M.D.*
Ann Arbor, Michigan

*Summary of Parke-Davis Award Lecture. Young & Rubicam, Inc., Detroit, Michigan.

Aortic Coronary Bypass*

A Review of 72 Cases

JOSEPH J. GARAMELLA, M.D., Ph.D., N. K. JENSEN, M.D.,
W. R. SCHMIDT, M.D., M. F. LYNCH, M.D., A. M. BILGUTAY, M.D., Ph.D.,
W. D. KELLY, M.D., Ph.D. and H. G. PINEDA, M.D.

THE DEVELOPMENT of cine coronary arteriography by Sones and Shirey,[1] allowing clear demonstration of pathologic anatomy, varying degrees of stenoses and/or occlusions which may be segmental or diffuse, led to improved accuracy in the diagnosis of coronary heart disease and paved the way for the clinical application of direct coronary artery surgery as a method of myocardial revascularization, supplanting many indirect methods.[2]

*Presented at the meeting of the Minnesota Surgical Society Mayo Clinic, Rochester, Minnesota. May 1, 1970.

At the present time, aortic coronary bypass with the use of reversed autogenous saphenous vein[3,4,5,6,7,8] appears superior to techniques with patch or interposition grafts. The immediate function of an aortic coronary bypass is highly attractive to patient, cardiologist and surgeon, and while needing no defense in concept, long-term evaluation will be necessary to determine the patency and behavior of such grafts. The symptomatic improvement in many of the patients undergoing aortic coronary bypass is

TABLE I
Direct Coronary Procedures

	Number	Mortality
A. Aortic Coronary Bypass		
1. To Right Coronary Artery	37	6
a. With no other procedures	9	0
b. With single mammary artery implant	8	1
c. With double mammary artery implant	18	4
d. With aortic valve replacement	1	0
e. With left anterior descending to right coronary bypass	1	0
2. To Left Anterior Descending Coronary Artery	18	3
a. With no other procedures	7	1
b. With single mammary artery implant	5	0
c. With double mammary artery implant	1	1
d. With mitral valve replacement	2	1
e. With ventricular aneurysm resection or suture	2	0
f. With closure of atrial septal defect	1	0
3. To Circumflex Coronary Artery	2	0
a. With no other procedures	1	
b. With single mammary artery implant	1	
4. To Left Anterior Descending and Right Coronary Arteries	10	2
a. With resection of aneurysm	1	0
b. With no other procedures	8	2
c. With single mammary implant	1	0
5. To Circumflex and Left Anterior Descending Coronary Arteries	2	1
a. With no other procedures	2	1
B. Right Coronary Interposition Graft	1	0
C. Coronary Endarterectomy	3	0
1. With Aortic to Right Coronary Bypass and Single Implant	1	
D. Gas Coronary Endarterectomy	3	0
1. With Aortic to Left Anterior Descending Graft	2	
2. With Single Implant	1	

striking, but inasmuch as the progression of underlying arteriosclerotic disease process is not modified, here too, long-term survival studies of operated patients will be necessary to clearly define the results.

It is the purpose of this report to present our clinical experiences with 74 cases of direct coronary surgery from September 26, 1968, to May 1, 1970.

Indications

Surgery was recommended if there was significant stenosis (60-75%) or occlusion of one or more of the three major coronary arteries demonstrated by arteriography associated with: (1) disabling angina; (2) previous myocardial infarction; (3) symptoms relating to chronic ventricular malfunction due to aneurysm, dyskinesia or akinesia.

In addition, there has been a small number of patients whose abnormal electrocardiograms, resting or exercise, have led to coronary arteriography which in turn demonstrated significant coronary artery disease. In selected cases, surgery was recommended and done.

Clinical Material

From September 26, 1968, to May 1, 1970, 74 patients have undergone direct coronary surgery. There were 72 cases of aortic coronary bypass alone or with an associated procedure. One interposition graft and one gas endarterectomy with an internal mammary artery implant were also done. The type, numbers and combinations of procedures are shown in Table 1.

In Table 2, the total experience with myocardial revascularization since 1964 is shown,

TABLE 2

Year	Total	Single Mammary Artery Implant	Double Mammary Artery Implant	Gastro-Epiploic Artery Implant	Direct Coronary Surgery	Ventricular Aneurysm	Deaths	Mortality Rate: Operative and Post-operative	Mortality Rate: Late
1964	3	3	0	0	0	0	2 (P-E 2)	66.7%	
1965	6	6	0	0	0	0	1 (L 1)		16.7%
1966	9	3	6	6	0	0	3 (S 1) (P-E 2)	33.3%	
1967	67	5	61	3	0	0	18 (S 1) (P-E 5) (P-L 3) (L 9)	13.5%	13.5%
1968	71	6	65	0	2	0	11 (S 1) (P-E 2) (P-L 2) (L 6)	7%	8.4%
1969	113	8	86	1	45	8	17 (S 6) (P-E 6) (P-L 3) (L 2)	13.3%	1.7%
1970	33	6	3	0	27	4	2 (S 2)	7.4%	
Total	302	37	221	10	74	12	57		

Day of Surgery = S
Postoperative, early = P-E, 1-15 days
Postoperative, late = P-L, 15-30 days
Late = L, 31 days or more

comprising 302 patients. Note the shift from indirect procedures to direct procedures between 1968 and 1970. Whereas there were two direct procedures and 71 indirect in 1968, there were 45 direct procedures in 1969, and 27 in a four-month period in 1970. Mortality rates for combined direct and indirect procedures for the respective years are shown.

Age and Sex

Patients ranged from 34 to 73 years. The distribution by decades is shown in Table 3. There were 62 males and 12 females.

TABLE 3
Age Distribution of Patients
Direct Coronary Surgery

Age	No. Patients
31-40	3
41-50	27
51-60	30
61-70	12
71-80	2
	—
Total	74

Operative Technique

Aortic coronary bypass with the reversed autogenous saphenous vein was conducted with the following methods and measures: (1) Cardiopulmonary bypass with cannulation of superior and inferior vena cava via the right atrium. (2) For arterial return, cannulation of the femoral artery or the ascending aorta when arteriosclerotic disease of the femoral artery was encountered or suspected. (3) Normothermic perfusion, in most instances. (4) Venting of the left ventricle. (5) Electrical fibrillation of the heart to render the field quiet. (6) Distal anastomosis of saphenous vein to coronary artery with 6-0 or 7-0 suture material. The aorta was not cross-clamped nor was distal coronary perfusion employed. The segment of coronary artery being anastomosed was excluded between silk loops or fine vascular clamps. (7) Proximal anastomosis to the ascending aorta, partially occluded with vascular clamps, using 5-0 or 6-0 suture material. (8) Internal mammary artery implantation was done after the aortic coronary bypass but during cardiopulmonary bypass. Mammary artery dissection was done prior to cardiopulmonary bypass. (9) Other additional procedures as valve replacement, infarctectomy and aneurysm repair were carried out after the vein graft was completed. (10) In several instances, gas coronary endarterectomy[9] was performed in the distal right coronary artery to establish a suitable run-off for the aortic coronary bypass. (11) More recently, gas coronary endarterectomy has been carried out for the completely occluded right coronary artery. (12) Postoperatively, patients were generally supported with mechanical ventilation via a nasotracheal tube for six to 18 hours. Blood gases, direct arterial and venous pressures were monitored.

Schematic representations of aortic coronary bypass are shown in Figures 1, 2, 3, 4. A specimen removed from the right coronary artery by gas endarterectomy is shown in Figure 5.

Mortality

The mortality for direct coronary surgery, operative (S = day of surgery); postoperative, early (P-E = 1–15 days); postoperative, late (P-L = 15–30 days); and late (L = 11 months) over the three-year period is shown

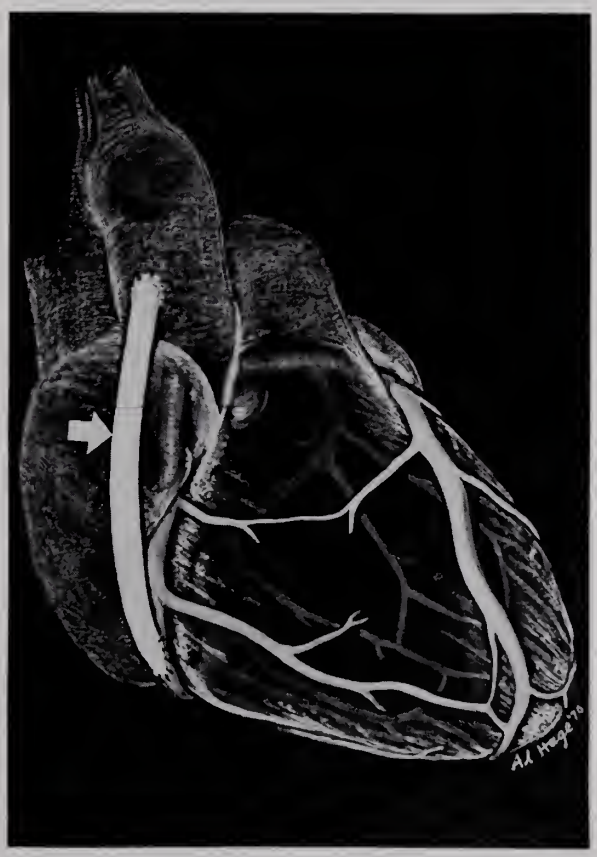


Fig. 1—Schematic drawings showing aortic coronary bypass to right coronary artery.

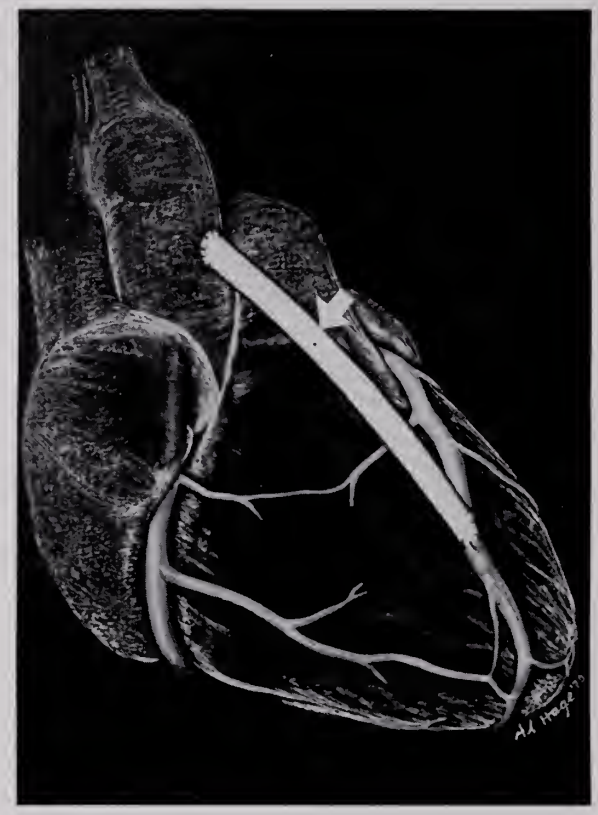


Fig. 2—Left anterior descending coronary artery.



Fig. 3—Right and left anterior descending coronary arteries.

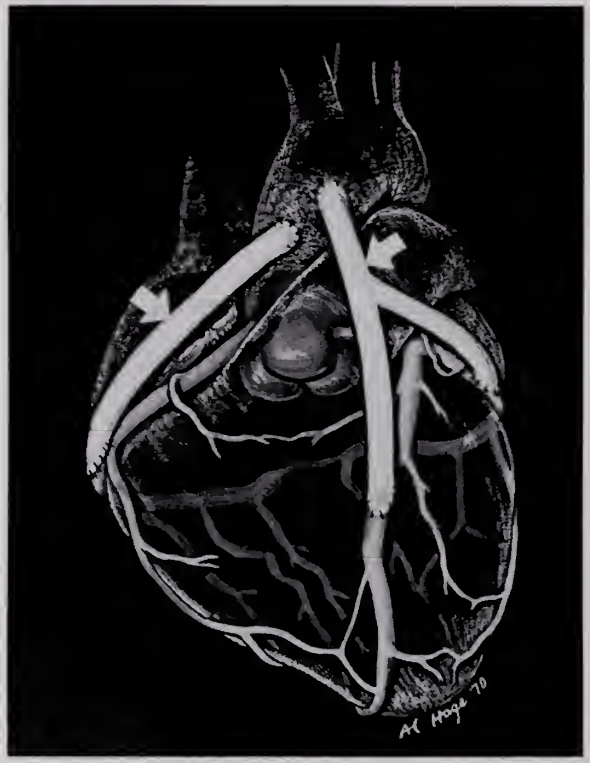


Fig. 4—Right, left anterior descending and circumflex coronary arteries.

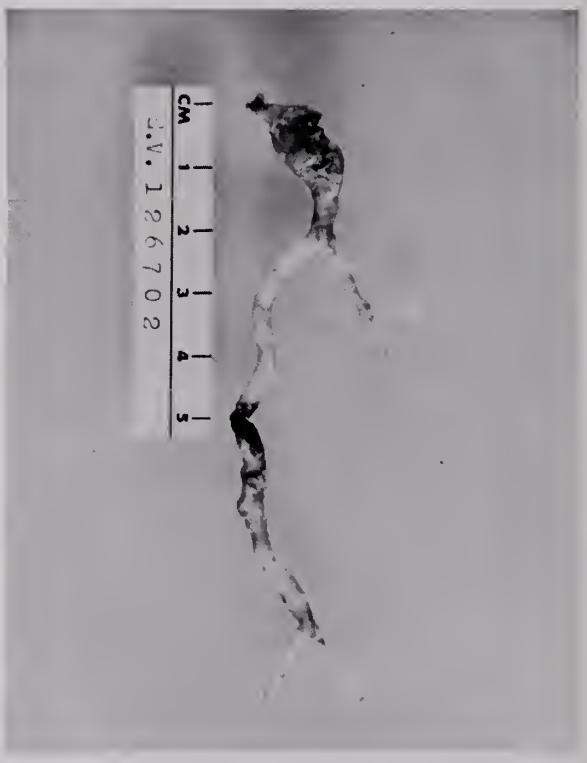


Fig. 5—Specimen of atherosclerotic cast of right coronary artery removed by the technique of gas endarterectomy.

in Tables 3, 4 and 5.

There were 12 deaths in 74 cases. Nine patients died in the operative or postoperative periods (12.2%). There were three late deaths (4%).

Causes of death were cardiac failure (seven), arrhythmia (two), pulmonary embolism (one), gastrointestinal bleeding due to stress ulcers and associated with myocardial infarction (one), and recurrent myocardial infarction occurring 11 months postoperatively (one).

Over a four-month period in 1970, 27 aortic coronary bypass operations have been done with two deaths (7.4%).

Discussion

Accurate delineation of the pathologic anatomy of coronary artery disease by coronary arteriography now permits clinical application of direct surgical procedures for myocardial revascularization. Presently, aortic coronary bypass with the use of reversed autogenous saphenous vein can be employed to alleviate stenotic

TABLE 4
Operative and Postoperative Mortality
Aortic Coronary Bypass

No.	Age	Date	Procedure	Time of Death	Cause of Death
1	65	5-69	Aortic-LAD-BIMI	Operative	Cardiac failure
2	48	5-69	Aortic-Rt. BIMI	P.O. 1 day	Arrhythmia
3	50	7-69	Aortic-Rt. BIMI	Day of Surg.	Arrhythmia
4	57	7-69	Aortic-Rt. IMI	P.O. 1 day	Cardiac failure
5	58	8-69	Aortic LAD	P.O. 1 day	Pulmonary embolism Graft closed
6	59	9-69	Aortic-Rt. Rt.-LAD	Operative	Cardiac failure
7	63	11-69	Aortic-Rt. Aortic-LAD	P.O. 3 days	Multiple stress ulcers. Subhepatic abscess. Myocardial infarction
8	42	1-70	Aortic-CX Aortic-LAD	Day of surgery	Cardiac failure
9	61	1-70	Aortic-Rt. Aortic-LAD	Surgical	Cardiac failure

LAD = Left anterior descending coronary artery
BIMI = Bilateral internal mammary artery implant
RT = Right coronary artery
IMI = Internal mammary artery implant
CX = Circumflex coronary artery
P.O. = Postoperative

TABLE 5
Delayed Operative Mortality
Aortic Coronary Bypass

No.	Age	Date Surgery	Procedure	Time of Death	Cause of Death
1	47	2-69	Aortic-Rt. BIMI	6 mos. postop.	Cardiac failure Progression of disease
2	55	5-69	Aortic-LAD and mitral replacement	45 days postop.	Cardiac failure
3	65	2-69	Aortic-Rt. BIMI	11 mos. postop.	Restudied eight mos. postop. Graft open. LAD closed. Myocardial infarction.

RT = Right coronary artery.
BIMI = Bilateral internal mammary artery implant.
LAD = Left anterior descending coronary artery.

or obstructive lesions in any of the major coronary arteries, singly or combined. In selected cases, this operation may be combined with other procedures as internal mammary artery implantation, valve replacement, infarctectomy or aneurysmectomy. Considering the severity of clinical problems, an operative and postoperative mortality of 12.2% seems acceptable.

The reduced mortality, 7.4%, two of 27 cases in 1970, suggests that improved patient selection, refinement in techniques and broadening total experience with the clinical and surgical problems may further improve results. Long-term follow-up will be necessary to establish the effect on patient survival. If possible and practical patients are returned for re-study of the aortic coronary graft in approximately one year. The arteriographic results of such a graft are shown in Figure 6.

Summary and Conclusions

1. From September 26, 1968, to May 1, 1970, 74 patients have undergone direct coronary surgery. There were 72 cases of aortic coronary bypass with reversed autogenous saphenous vein.

2. Indications for surgery and the operative technique with cardiopulmonary bypass have been outlined.

3. The technique of gas endarterectomy is being employed and merits further trial and analysis.

4. There were nine operative and postoperative deaths (12.2%) and three late deaths (4%).

5. In 1970, in a four-month period, there have been two deaths in 27 cases (7.4%).

6. Long-term follow-up is necessary to determine graft patency and behavior, and also the effect on patient survival.

Addendum

Since the submission of this manuscript to November 1, 1970, an additional 76 patients have undergone aortic coronary bypass with the use of the reversed autogenous saphenous vein. Twelve procedures were single aortic coronary bypasses. The others were double bypasses or combined with internal mammary artery implants, valve replacements, resection of ventricular aneurysm, closure of atrial septal defects and gas (carbon dioxide) coronary endarterectomy. There were nine (9) (11.8%) operative and postoperative deaths (within 30 days).



Fig. 6—Arteriographic study one year after surgery showing the patent aortic coronary bypass graft with filling of the right coronary artery distal to the anastomotic site.

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Idiopathic Pulmonary Hemosiderosis

Two-and-One-Half-Year Follow-up in an Adult

WILLIAM L. HEDRICK, M.D.*

IDIOPATHIC PULMONARY hemosiderosis, once thought to be a medical rarity, has become increasingly common, as it has been considered in the differential diagnosis of pulmonary disease.[1]

The first report of this entity was by Virchow in 1864, and it was re-introduced to the literature by Ceelan in 1931. The first case in an adult was reported by Waldenstrom in 1940. A case with follow-up is presented here because it is felt to be of interest in diagnosis and therapy and in the patient's course over a two-and-one-half-year period.

Case Report

The patient, a 19-year-old male ballet dancer, was first seen June 20, 1967. His chief complaint was easy fatigue, dyspnea on exertion, occasional night sweats and a cough with streaks of blood on two occasions, not having recurred, however, in the two weeks prior to his initial visit. There was no hematuria during the current illness or previously.

There had been occasional episodes of pyrosis in the past, and the patient had previously received a deferment from military service because of a cardiac murmur.

A physical examination showed a well-nourished, well-developed white male who appeared to be chronically ill and pale; height 5′ 7″; weight 136 pounds; temperature 98.8 degrees F. There were shot-like cervical nodes anteriorly and posteriorly. Inguinal adenopathy of a minimal degree was also noted. A systolic murmur 2/6 was heard at the base of the heart. Examination of the lungs revealed rales at the anterior base of the right chest. The rest of the examination was within normal limits.

The patient's initial hemoglobin was 8.5 Gm and the red cells appeared normochromic and normocytic. The other blood elements were normal.

He was admitted to the hospital at this time. The initial chest x-ray (Figure 1) showed an infiltrate in the right lower area, giving the impression that he might have a mycoplasma pneumonia with secondary hemolysis or gastrointestinal bleeding. The initial reticulocyte count was 4.2%; a repeat was 7.1%. Heterophile titer, a lupus



Figure 1



Figure 2

*Department of Internal Medicine, St. Mary's Hospital, Minneapolis, Minnesota.

erythematosus clot test and a Coombs' test were negative. Cold agglutinins were absent. There was no evidence of blood loss. His proctoscopic examination, colon and stomach x-rays were essentially normal. It was apparent, on a peripheral smear later, that he was developing a hypochromic anemia. His serum iron was down to 32 mcg% with an iron binding capacity of 380 mcg% (saturation, 8.4%). His chromium 51 red cell survival was reduced to a half life of 21 days (normal, 25-35 days). There was, however, no increased pickup of the chromium 51 over the thoracic cavity.

A second chest x-ray (Figure 2) revealed an infiltrate in the left lower lung field as well as the previous changes on the right side. There was no evidence of microscopic hematuria. A diagnosis of idiopathic pulmonary hemosiderosis was then considered. Subsequently his sputum was positive for hemosiderin-laden macrophages (Figure 3). Pulmonary biopsy (Figures 4 and 5) revealed thickening of the alveolar septum, chronic inflammation and fibroblastic organization, with large masses of hemosiderin-laden macrophages in the alveoli but no evidence of vasculitis. These facts were considered indications of and compatible with pulmonary hemosiderosis.

The patient had an uneventful postoperative course and was started on oral iron. His hemoglobin returned to normal and he has since done well. His chest x-ray (Figure 6) has completely cleared, and his pulmonary function studies (Table) have remained within normal limits. He has resumed dancing on a full-time basis and is not limited in activity. However, he has continued to have hemosiderin-laden macrophages in his sputum. He has not taken oral iron over the last two years and there has been no recurrence of his anemia. His heart murmur disappeared with the treatment of his anemia. His serum electrophoretic pattern was normal in November 1969, and his immunoglobulins were also within normal limits. His IgM was 60 mgs%; his IgA, 350 mgs% and his IgG, 900 mgs%.

TABLE
Pulmonary Function Studies

Studies	Normal	10/67	7/68	11/69
FEV_1	3670 cc	3265	3375	3490
FEV_T	4420 cc	4805	5020	5155
MVV	134 L/min	157	172	167
RV	1905 cc	1580	1827	1297
TLC	6325 cc	6275	7012	6397
RV/TLC	30%	25	26	31
D_L CO	33.8 cc/min	—	33.4	41.9
pH	7.36-7.40	7.38	7.43*	7.41†
$PaCO_2$	38-42	38	39	40
PaO_2	90-100	94	88	89
SaO_2	97%	9.69	96	96

*Before exercise 7/68
†After exercise 7/68

Discussion

Idiopathic pulmonary hemosiderosis typically occurs in a young person with a history of hemoptysis, a lung infiltrate and a hypochromic anemia. The disease has a variable and individual course. The anemia is usually hypochromic, but initially it may be both normocytic and normochromic, as in the present case. With the usual reticulocyte elevation this may be mistaken for hemolysis. Iron is lost into the parenchyma of the lungs and is not utilized de-

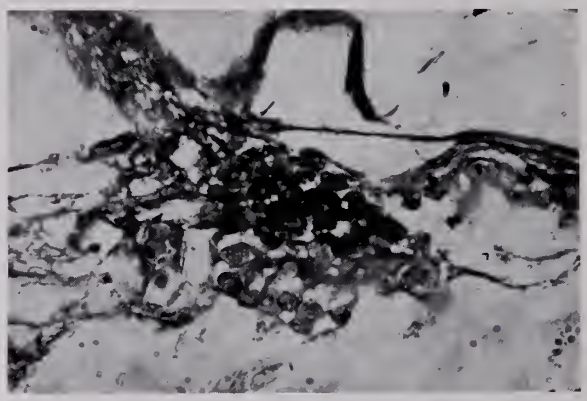


Figure 3

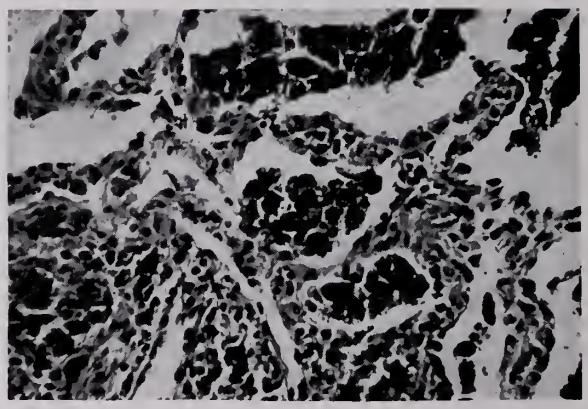


Figure 4

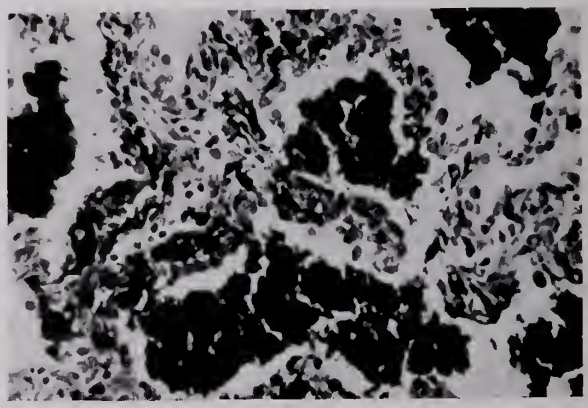


Figure 5

spite iron deficiency.[2] This is felt to be a disease of abnormal alveolar histology and function with secondary capillary bleeding.[3] One third of the iron 59 labeled red blood cells can be lost into the lung.[4]

The x-ray findings typically show diffuse ground glass infiltrate, either single or multiple,[5] which can be asymptomatic without coughing or hemoptysis. This disease can occur without any x-ray changes at all and also without anemia. The major pulmonary finding generally shows a reduction of the diffusion capacity of carbon monoxide. On a one-year follow-up Aledort and Lord[6] report that the diffusing capacity in their case did decrease despite the fact that clinically the patient was unchanged. However, as their patient did have microscopic hematuria, one would conclude that this was probably a case of Goodpasture's syndrome.

The clinical course is extremely variable in this disease. There are patients who have survived for more than twenty years. Sudden death can occur,[7] however, and has been compared to a salt-water drowning, with the patient sanguinating into his own pulmonary tract.[8] In the disability of long-term survivors with this condition, chronic fibrosis may be a mechanism.

The etiology of idiopathic pulmonary hemosiderosis is essentially unknown; there is the possibility, however, of autoimmunity playing a role. More recently some consideration has been given to milk allergens, without definite proof, however. Recently a case of deficiency of $Alpha_1$ antitripsin was reported in idiopathic pulmonary hemosiderosis.[9] Also, patients with idiopathic pulmonary hemosiderosis have been reported to demonstrate immunoglobulin abnormalities with reduced IgA.



Figure 6

The presumptive diagnosis of idiopathic pulmonary hemosiderosis can be made by the clinical history coupled with either laboratory findings of sputum-positive hemosiderin-laden macrophages or with gastric aspirant containing the same macrophages laden with hemosiderin. The definitive diagnosis, however, is made by pulmonary biopsy. More recent studies have shown that the linear profile scan utilizing radioactive iron may yet prove to be specific for this disease.[4]

The following conditions must be excluded in the differential diagnosis: mitral stenosis, Goodpasture's syndrome, vasculitis, congestive heart failure, bronchiectasis and tuberculosis. Several cases have been called idiopathic pulmonary hemosiderosis in the literature which had been associated with gross or microscopic hematuria; but these patients have to be considered as having Goodpasture's syndrome, not idiopathic pulmonary hemosiderosis. This distinction is important since the course, management and prognosis are considerably different in these two entities.

A recent discussion[10] describes treatment by intermittent positive pressure breathing to sustain the patient over a severe episode of intrapulmonary bleeding. Steroids have also been used in the acute situation with somewhat equivocal results, but they do probably merit use in such an emergency. Splenectomy has been tried without any significant success. The iron chelator desferrioxamine has been used but is not beneficial, because the iron cannot be mobilized from the pulmonary parenchyma. Oral iron has been used in order to treat the anemia, since the iron that is lost in the tissue is not available for reutilization in hemoglobin synthesis.

The present case is of interest because initially it was thought that the patient had either hemolysis or acute blood loss; but later it was evident that there was chronic blood loss pres-

ent. There was very little hemoptysis on direct questioning; but, when considered in perspective, this is a fairly typical case of idiopathic pulmonary hemosiderosis. With the murmur one wonders if perhaps this patient did not have an episode of anemia with a flare of idiopathic pulmonary hemosiderosis at the time he failed the selective service examination. It is of interest that he has had a two-and-one-half-year follow-up and has continued to have sputum positive for hemosiderin-laden macrophages on several occasions without clinical evidence of disease on roentgenographic study or by pulmonary function study.[11,12] Also of interest is the fact that he had normal levels of immunoglobulins.

Summary

A case of a 19-year-old male with idiopathic pulmonary hemosiderosis has been presented. The patient has survived two and a half years after the initial episode.

It is of further interest that idiopathic pulmonary hemosiderosis can persist with low-grade activity in the absence of clinical or laboratory findings other than the persistence of the hemosiderin-laden macrophages. Probably the hallmark of this disease is its variability of symptoms, signs and clinical course. It will be of interest to follow this patient in the future. So far he has done well with a minimum amount of treatment, but perhaps we may be seeing only the surface of the "iceberg." Idiopathic pulmonary hemosiderosis is still infrequently diagnosed, poorly understood and inadequately treated.

Addendum

The patient was last seen during the summer of 1970, and was in excellent health at that time. He is presently functioning normally without symptoms.

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Collet-Sicard Syndrome

The features of this syndrome consist of unilateral involvement of the ninth, tenth, eleventh, and twelfth cranial nerves. Paralysis of the vocal cord and palate, loss of taste over the posterior third of the tongue, hemianesthesia of the larynx, pharynx, and palate as well as paralysis of the trapezius and sternocleidomastoid muscles are characteristic features. Collet (1915) described the syndrome as "glossolaryngoscapulopharyngeal hemiplegia," Vernet (1916) as "the complete syndrome of the last four cranial nerves," and Sicard (1917) as the "syndrome of the condyloposterior lacerated foramen." Etiology may follow trauma (as from a bullet) in the posterior cranial fossa, a localized meningitis, or tumor.

Durham, Robert H.—Encyclopedia of Medical Syndromes
Hoeber Medical Division, Harper and Row, New York



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Numerous investigators have remarked on the high degree of effectiveness of Lomotil in a variety of diarrheal disorders. Lomotil has given good to excellent relief of symptoms in many patients who had failed to respond to other measures.

UNSURPASSED ANTIDIARRHEAL ACCEPTANCE
Patients prefer Lomotil for its convenience, its prompt control of diarrhea and its relief of cramping and urgency. Physicians specify Lomotil for its dependable action and its relative freedom from side effects when taken as directed.

Warnings: Lomotil should be used with caution in patients taking barbiturates and, if not contraindicated, in patients with cirrhosis, advanced liver disease or impaired liver function.

Precautions: Lomotil is a federally exempt narcotic with theoretically possible addictive potential at high dosage; this is not ordinarily a clinical problem. Use Lomotil with considerable caution in patients receiving addicting drugs. Recommended dosages should not be exceeded, and medication should be kept out of reach of children. Signs of accidental overdosage may include severe respiratory depression, flushing, lethargy or coma, hypotonic reflexes, nystagmus, pinpoint pupils, tachycardia; continuous observation is necessary. The subtherapeutic amount of atropine sulfate is added to discourage deliberate overdosage.

Adverse Reactions: Side effects reported with Lomotil therapy include nausea, sedation, dizziness, vomiting, pruritus, restlessness, abdominal discomfort, headache, angioneurotic edema, giant urticaria, lethargy, anorexia, numbness of the extremities, atropine effects, swelling of the gums, euphoria, depression and malaise.

Overdosage: The medication should be kept out of reach of children since accidental overdosage may cause severe, even fatal, respiratory depression.

Dosage: The recommended initial daily dosages, given in divided doses until diarrhea is controlled, are as follows:

Children:

3-6 mo. .. ½ tsp.* t.i.d. (3 mg.)
6-12 mo. .. ½ tsp. q.i.d. (4 mg.)
1-2 yr. ... ½ tsp. 5 times daily (5 mg.)
2-5 yr. ... 1 tsp. t.i.d. (6 mg.)
5-8 yr. ... 1 tsp. q.i.d. (8 mg.)
8-12 yr. .. 1 tsp. 5 times daily (10 mg.)
Adults: ... 2 tsp. 5 times daily (20 mg.)
or 2 tablets q.i.d.

*Based on 4 cc. per teaspoonful.

Use of Lomotil is not recommended in infants less than 3 months of age.

Maintenance dosage may be as low as one-fourth the initial daily dosage.

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Indications: Edema associated with congestive heart failure, cirrhosis of the liver, the nephrotic syndrome, late pregnancy; also steroid-induced and idiopathic edema, and edema resistant to other diuretic therapy. 'Dyazide' is also indicated in the treatment of mild to moderate hypertension.

Contraindications: Pre-existing elevated serum potassium. Hypersensitivity to either component. Continued use in progressive renal or hepatic dysfunction or developing hyperkalemia.

Warnings: **Do not use dietary potassium supplements or potassium salts unless hypokalemia develops or dietary potassium intake is markedly impaired.** Enteric-coated potassium salts may cause small bowel stenosis with or without ulceration. Hyperkalemia (>5.4 mEq/L) has been reported in 4% of patients under 60 years, in 12% of patients over 60 years, and in less than 8% of patients overall. Rarely, cases have been associated with cardiac irregularities. Accordingly, **check serum potassium during therapy, particularly in patients with suspected or confirmed renal insufficiency (e.g., certain elderly or diabetics). If hyperkalemia develops, substitute a thiazide alone. If spironolactone is used concomitantly with 'Dyazide', check serum potassium frequently**—they can both cause potassium retention and sometimes hyperkalemia. Two deaths have been reported in patients on such combined therapy (in one, recommended dosage was exceeded; in the other, serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving Dyrenium (triamterene, SK&F). Rarely, leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with the thiazides. Watch for signs of impending coma in acutely ill cirrhotics. Thiazides are reported to cross the placental barrier and appear in breast milk. This may result in fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism and possibly other adverse reactions that have occurred in the adult. When used during pregnancy or in women who might bear children, weigh potential benefits against possible hazards to fetus.

Precautions: Do periodic serum electrolyte and BUN determinations. Do periodic hematologic studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in postsympathectomy patients. The following may occur: hyperuricemia and gout, reversible nitrogen retention, decreasing alkali reserve with possible metabolic acidosis, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), digitalis intoxication (in hypokalemia). Use cautiously in surgical patients. Concomitant use with antihypertensive agents may result in an additive hypotensive effect.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis; rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting (may indicate electrolyte imbalance), diarrhea, constipation, other gastrointestinal disturbances. Rarely, necrotizing vasculitis, paresthesias, icterus, pancreatitis, and xanthopsia have occurred with thiazides alone.

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Editorials

Hypergammaglobulinemia*

THE INTERESTING REPORT from the Mayo Clinic by Dr. Paul Hermans points out once again the rather limited usefulness of serum protein electrophoresis. The diseases which he reports as being associated with increased amounts of gamma globulins are the same clinical conditions which have been reported in the past to be associated with large amounts of gamma globulins as demonstrated by protein electrophoresis. The first clue to hypergammaglobulinemia should, of course, be an elevated total protein value; most authorities would recommend that any serum protein over 8 grams % should be further investigated. However, there are individuals with serum proteins of this value who are in perfect health, generally young adult males. The clinical laboratory should be able to assist in the delineation of pathological proteins, using immunoelectrophoresis† and immuno-diffusion techniques.

The increase in the total serum protein is almost always due to an increase in the gamma globulins, and this increase in turn is almost always due to an increase in the gamma G molecules. Many times the gamma A and gamma M moieties are increased as well; but unless they are extremely elevated they are not usually reflected in the ordinary electrophoretic pattern. Protein electrophoresis can suggest whether the hyperproteinemia is due to a polyclonal‡ or monoclonal# gammopathy, and further studies can be undertaken with immunoelectrophoresis to delineate the nature of the pathological protein. A specific diagnosis can be made in some instances with immunoelectrophoresis, particularly when dealing with multiple myeloma or Waldenstrom's macroglobulinemia. There are instances when a monoclonal gammopathy is associated with diseases other than multiple myeloma, and these would include carcinomas, particularly of the colon, and lymphomas of any type. There are also instances of monoclonal peaks in individuals who have no demonstrable disease ("benign monoclonal gammopathy").

Protein electrophoresis is a helpful tool when faced with either hyperproteinemia or hypoproteinemia, and gives some indication that specific procedures should be undertaken to aid in the diagnosis. Immunoelectrophoresis and immunodiffusion can be of inestimable help

*Hermans, Paul E.: Massive Diffuse Hypergammaglobulinemia. Minnesota Med 52:1615, 1969.

†Immunoelectrophoresis: A technique in which serum proteins are first separated in an electric field. Antibodies are then added and precipitation occurs where the specific antigen encounters the specific antibody. Up to thirty proteins have been identified in this way. Agar gel is a commonly used medium.

‡Polyclonal: The broad-based gamma-globulin fraction seen on paper electrophoresis. The complex is heterogeneous, not sharply peaked, and reflects an increase in several of the immunoglobulins usually.

#Monoclonal: A sharp peak seen in the gamma-globulin area on paper electrophoresis. It represents the elaboration of electrophoretically and antigenically homogeneous immunoglobulin (G, M, A or D) or excessive quantities of comparably homogeneous polypeptide subunits of these proteins. There is usually an associated deficiency in the synthesis of the normal immunoglobulins.



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in detecting deficiencies or the absence of any of the specific immunoglobulins, gamma G, gamma A, gamma M or gamma D. There are also specific antisera available to react with single antigens, such as transferrin, ceruloplasmin, haptoglobin, alpha-2 macroglobulin, beta-lipoprotein, complement, pre-albumin and others. These techniques have greatly expanded our ability to detect specific protein abnormalities. Also, immunoelectrophoresis is often the only way Bence-Jones proteins can be detected. This is especially useful when the serum electrophoresis is normal or even shows decreased gammaglobulins and the patient has circulating Bence-Jones proteins in the serum ("Light-chain disease") or is excreting Bence-Jones proteins in the urine in small but abnormal amounts, undetectable by the usual insensitive qualitative tests.

Serum protein electrophoresis of itself can only be moderately helpful in most cases, and as long as the techniques are available for more careful scrutiny of abnormal proteins, these should be undertaken. Immunoelectrophoresis and immunodiffusion are certainly within the province of the clinical laboratory and are not particularly difficult procedures. The more refined techniques such as ultracentrifugation can also be performed in reference laboratories if the physician feels that this is required.

Paul R. Finley, M.D.*
Minneapolis, Minnesota

*Clinical Pathologist, Fairview Hospital.

Squamous Cell Carcinoma of the Oral Cavity*

EVERY PATIENT with cancer of the oral cavity should be considered as presenting an individual problem. There should be no rigidity in approach and no hard and fast rules concerning treatment. These cancers occur in all varieties of patients and are so varied in their gross extent, location, type, and infiltration that anyone who undertakes their treatment should be familiar with the many approaches available to the head and neck cancer surgeon and also with the skills and accomplishments of the modern expert radiotherapist. He should be able to provide the best that medicine can give from the beginning and should be willing to see the problem through to the bitter end.

Farley has presented a case report of a single patient with a cancer in the floor of the mouth. His report serves to emphasize the desire to cure and to minimize cosmetic and functional deformity. In discussion with the patient it is the duty of the physician to stress that the desire to cure must be considered primary and that to minimize deformity secondary. Farley's report also serves to emphasize that compromise between these two deviant wishes is ever present, unavoidable, and not undesirable.

Kenneth D. Devine, M.D.
Rochester, Minnesota

*Farley, H. H.: Squamous Cell Carcinoma: Anterior Floor of the Mouth. Minnesota Med 53:131, 1970.

Hypoxia, Hypercarbia and Respiratory Acidosis

DR. WANG* HAS provided us with a timely review of the acid-base abnormalities that constitute the basis for respiratory therapy. Although most modern systems for the determination of arterial CO_2 tensions are equipped with oxygen electrodes, a significant number of institutions still use the Astrup equilibration technique. When carried out properly on an arterial blood sample, this technique is capable of providing the clinician with accurate information regarding pH, P_{aCO_2}, buffer base, and base excess, but does not provide information about oxygen partial pressure, or percent of hemoglobin oxygen saturation.

*Wang, J. K.: Acid-Base Balance Abnormalities in Respiratory Therapy. Minnesota Med 53:957, 1970.

Although one can estimate the approximate maximal $P_{a_{O_2}}$ possible with a given $P_{a_{CO_2}}$ while a patient is breathing air, one may be given a false feeling of security by this estimation when so many patients with respiratory insufficiency are suffering from significant maldistribution of ventilation and perfusion, or venous admixture. In this situation the relationship is no longer predictable and severe degrees of arterial hypoxemia may exist with the absence of reliable clinical signs.

The obvious solution to this problem is the simultaneous measurement of both oxygen and carbon dioxide tension and pH in arterial blood, with the patient breathing a precisely known gas mixture, usually either air or 100% O_2 by a non-rebreathing system. One may then assess the alveolar-to-arterial gradient and the degree of right-to-left shunting.

Although hypoxemia and acidosis are potentially lethal, hypercarbia in the absence of severe acidosis or hypoxemia is not. Therefore one should direct the therapy to the abnormality with the highest risk. Additional oxygen is appropriate treatment for hypoxemia. Buffers such as THAM and sodium bicarbonate are effective in managing the acidosis. Of these two, sodium bicarbonate is the most frequent choice because of its great margin of safety. One must be aware of the sodium equivalency of this buffer, realizing that some patients may be incapable of excreting efficiently the extra dose of cation. THAM, on the other hand, frequently causes respiratory depression, and even apnea, in patients with respiratory insufficiency, and facilities should be on hand to support ventilation when it is used.

Edward P. Didier, M.D.
Rochester, Minnesota

Coronary Detours

Since Favaloro's report in 1968[1] describing the use of an autogenous piece of saphenous vein to bypass coronary vessel obstruction, thousands of such operations have been performed on patients with coronary disease.[2,3] The public enthusiasm may be said to be at fever pitch[4] in spite of (possibly because of) the novelty of the operation. One report of a small group of patients (35) states that 74% (26) are markedly improved with minimal or no angina.[5] However, the surgery is of imposing magnitude with significant mortality and morbidity, and its place in the therapy of coronary disease depends primarily upon significant increase in longevity. The procedure has not yet come of age for such evaluation.

Although coronary disease is never minimal, the post-myocardial infarct patient who survives his attack to leave the hospital without symptoms has a reasonably good prognosis; 94% will survive the first year.[6] Subjecting him to an operation that carries a mortality up to 21% is not justifiable. The operation is still in the experimental stage only three years after its introduction and should be tried out on patients who suffer from their disease, not on those carrying on their daily functions without symptoms. Garamella et al.* apparently consider as surgical candidates patients who have had a myocardial infarction and show angiographic evidence of coronary occlusion without symptoms. This experimental procedure must prove its merit upon patients who are ill with their disease. Much more study is necessary, showing, for instance, the relationship of relief to patency of the graft a year or so after surgery.

The Garamella group reports an eight-month experience with 12 deaths in 74 cases (16.2%). In their second four months the mortality was reduced to two deaths in 27 cases (7.4%). For those preparing to embark upon this surgical procedure, consider the mortality statistics that can be derived from the above figures for their first four months' experience: 10 deaths in 47 patients (21.3%).

Reuben Berman, M.D.
Minneapolis, Minnesota

*See page 1227.

References may be secured from the author or the reprints.

You May Be Right

MINNESOTA MEDICINE—At the Cross Roads

The present state of confusion and lack of knowledge of our membership is aptly illustrated in a recent issue of the Hennepin County Medical Bulletin. Here one reads that the recent hike in the annual dues of the State Society is due in part to some financial difficulty of MINNESOTA MEDICINE. A glance at the November and December issues of MINNESOTA MEDICINE reveals the lowest quantitative level of communication of medical science in a decade. What is happening? Has there been a slump in the income of physicians? Has the well-spring of science in Minnesota dried up? Possibly, the glitter of the dollar has overshadowed the guiding light of the Hippocratic Oath "teach thy brother-physician."

Let us consider a few of the basic facts. At the last House of Delegates meeting in June of 1970 your representatives decided to cut the long-standing budget of your Journal, despite the rising costs, by reducing that portion of your dues going to MINNESOTA MEDICINE, from approximately $11.50 to $7.50 per annum; this loss to the Journal must be added to two other little known burdens loaded onto its apparent cost. These include a sizable allocation of the salary of the Executive Secretary of the Society and the cost of printing the annual Roster of the State Society.

Possibly there is a reason for fooling others but let us not deceive ourselves. MINNESOTA MEDICINE is the one universally visible banner of medical science portrayed by our State Society. Even the great silent majority of our membership who haven't contributed an hour of their post-graduate life to advancing medical science, but have given their token contribution to its cost of publication, could take pride in the success of MINNESOTA MEDICINE. This pride will soon change to shame or loss of interest unless you start talking and writing.

Arthur H. Wells, M.D.
Duluth, Minnesota

MINNESOTA MEDICINE—November

Needless to say, although I certainly want to say it, I was horrified to see the last issue of MINNESOTA MEDICINE, the remnant of a once proud, and great state medical journal. If this is what "living within the budget" means, then I think it is high time the entire situation is reviewed.

As far as I am concerned, MINNESOTA MEDICINE has reached its peak of greatness under the editorship of Carl O. Rice, and I think it would be a great pity to sabotage his efforts now. I, for one, would rather pay a bit more dues than to have our journal go to pot this way. I sincerely hope this can be rectified.

I am aware, of course, that Carl has done this deliberately to make his point, but he has certainly made it in such a way that all our membership will know what he is trying to do. I am also aware that the Council and officers have not always agreed with Carl, and certainly have not done so in the area of finance for the Journal. On the other hand, look what he has done for MINNESOTA MEDICINE. He and his board of editors have made it one of the outstanding state medical journals in the entire country, and you can't do this without spending some money, which I think we certainly ought to be able to afford.

You May Be Right (Continued)

I sincerely hope that this impasse between Dr. Rice and his board and our own official bodies, the Council, Officers, and House of Delegates can be settled in favor of the goals which Dr. Rice has been able to attain for all of us.

C. G. Sheppard, M.D.
Le Sueur, Minnesota

MINNESOTA MEDICINE—International

In conversations with visiting colleagues from the United States I was told that you have been having problems in your endeavors to maintain MINNESOTA MEDICINE in its present form and with its comprehensive contents.

I believe it would be extremely regrettable if this much-read professional medical journal, which owes so much to your personal efforts, should be in danger of perishing.

Like many of my colleagues in Bonn I am in the habit of reading the scientific contributions as well as those dealing with general medical viewpoints. All of us would certainly be very disappointed to see this valuable Journal disappear for it contains so much of importance for the general practitioner, as well as for the continuing education of the specialist. To discontinue its publication would mean a great loss, not only for the American but also for the international reader.

I attribute this widespread interest in MINNESOTA MEDICINE especially to you as it has meanwhile taken root in Europe as evidenced by the collaboration of colleagues from France, Switzerland and especially the Federal Republic of Germany. I know well with what seriousness and knowledge you have worked on the form and image of this very valuable medical journal and that you continue to do so. I wish you the very best of success in the future in your efforts to give the American readership an opportunity to inform themselves about present-day medical problems and progress in European medicine. Aside from being purely informative, it is more important that MINNESOTA MEDICINE continue on an international basis to provide mutual information which in this day and age is needed more than ever before.

Thus I am hopeful that you shall find the necessary understanding and help that will enable you to continue MINNESOTA MEDICINE in its present form. As for me and my co-workers, I promise to continue to provide you with contributions as best as we can.

With the best wishes for success in your endeavors and friendly esteemed greetings from a colleague.

Professor Alfred Gutgemann, M.D.
Bonn, West Germany

Editor's Note: Professor Gutgemann is Head of the Department of Surgery, the University Medical School, Bonn, West Germany. Professor Gutgemann has also been elected to the prestigious position of President of the German Surgical Society earlier this year, an honor for which MINNESOTA MEDICINE adds its congratulations.

*Translated from German, H. W. H.

You May Be Right (Continued)

MINNESOTA MEDICINE—West Berlin

I have just sent some newspaper clippings plus a set of the instructions concerning the possibility of having the medical people at the Rudolph Virchow University of Medicine, West Berlin, collaborate with Dr. Carl Rice in developing a series of original articles for MINNESOTA MEDICINE from that very old and noted school of medicine. We visited there when we were in West Berlin, as you will recall, and were quite impressed with their recent modernization of that medical school.

Will you send a copy of this last issue of MINNESOTA MEDICINE to Alex Hasenclever, so that he might see what was done by the people at the University of Giessen? I hope this will result in an issue similar to this current one some months in the future. What has happened to the financing of MINNESOTA MEDICINE?

I have been reading the letters and comments about it from others, which make me realize what a fine journal we have, and how very much it is appreciated by many of our members. I do hope it will continue as it has been, and that we continue to finance it adequately.

C. G. Sheppard, M.D.
Le Sueur, Minnesota

Short Cuts in Tuberculosis Care?

Not being a journalist, the enclosed paper cannot match your editorial excellence in MINNESOTA MEDICINE, for it cannot fit into the usual type of article you publish. However, as I hear the advice on care of tuberculosis by persons who do not actively treat the disease, it seems much is being done for tuberculosis by guess rather than by accepted medical study and treatment and on the basis of the individual's need. Our warnings are laughed out of court by those in power, for the care of tuberculosis is a form of socialized medicine in the state and nation.

Perhaps some of the problem stems from the acceptance of the misnomer "prophylactic chemotherapy" for primary tuberculosis, which is a very active form of the disease even though the patient does not know he is infected. Seeing the reduced morbidity and mortality, public health officials are satisfied, but the results would be better if the vast increase in knowledge of drugs were applied as it could and should be, tailored to each case when we have the means to do so.

For the past two decades irresponsible advice has been given physicians about treatment for tuberculosis. "Leave the new case at home. Isoniazid makes them all negative in a few weeks anyway." Nothing is said about the resistance of tubercle bacilli to isoniazid which develops in many patients after isoniazid is given alone for a few months; nor about how long to give the isoniazid; nor about the necessity of x-rays and cultures in diagnosis and follow-up once the disease becomes inactive.

Another statement tells doctors to give anti-tuberculosis drugs to all patients with x-ray evidence of tuberculosis even when inactive, if no previous, or "inadequate," chemotherapy has been given.

Dr. Kinsella resected cavitary lesions from some of our patients after the tuberculin test had become negative in those patients receiving the three primary drugs for tuberculosis. In many of these cases the

You May Be Right (Continued)

pathologist found tubercle bacilli on his slides and in the cultures. Presumably the drugs had not penetrated the scar tissue. When resection was not done, relapse often occurred in similar patients who had turned negative and for whom the drugs had been discontinued when the patients were thought well enough to be classified as inactive. Hence the decision to resect if enough functional lung remained.

A happy solution to the whole tuberculosis problem has been promoted by the United States Public Health: to give every positive Mantoux reactor in the country isoniazid for one year, so that the glad cry of "Eradicated!" can be sounded. Hopefully, some doctors will ask for the x-rays, cultures, and follow-up. But will not the happy expectation be shattered when some of those moderately too far-advanced cases, denying illness, find themselves doomed to failure after taking the isoniazid alone for only one year.

For those of us who learned how to use the anti-tuberculosis drugs the hard way, by having failures, until we gave the three antibiotic drugs concommitantly to the minimally, moderately and far-advanced cases for two, three or more years as their progress seemed to indicate, it was refreshing to note the Veterans Hospitals' completed study in 1967 wherein they found the three combined drugs the most effective.

William Lester of the National Jewish Hospital, Denver, Colorado, writes as one who has been working with tuberculosis. He believes that isoniazid initially was mis-used because of lack of supportive synergistic drugs. He has employed different regimens, compared results, and reported his conclusions for our guidance. He contends that prevention of further dissemination of the infection is valuable; that hospitalization for treatment failure is important; that two well-chosen drugs are not as effective as three for initial treatment, and he shows himself to be a concerned practitioner when he advocates that "failure should not be allowed to occur."

Lillian A. Olson, M.D., F.C.C.P.
Ah-Gwah-Ching, Minnesota

Loyal Friend

I was disturbed when I read the article about MINNESOTA MEDICINE dying. I get so much kick out of so many of the things you write and I look for the Editor's Soliloquy: The Social Hour, and Looking Backwards. I was glad to read J. Arthur Meyer's story in the Fifty-Year Group. He is such a fine gentleman. I have recently met a patient of his in Fort Myers who says that she is alive because of him. I give my copies to my dermatologist who seems so pleased to read MINNESOTA MEDICINE. I am sure that any doctor would be interested in reading it.

Mrs. George M. Tangen, Sr.
Ft. Myers, Florida

The Driver's Seat

I enjoyed and admired your "Soliloquy."* The points you make as to our future computerized medicine are in fact correct. I fear, however, that such protests come too late and that the ideals and ideas which you support are common to only a very small number of us.

Integrity of character, self-respect and intellectual honesty have been deemed amusing by doctrinaire theoreticians in our Ivoried Halls. There seems to be

You May Be Right (Continued)

a group which has tacitly agreed that the way to keep themselves in the driver's seat is to make full and frequent use of Hitler's big lie technique. This group appears to have brainwashed a sufficient number of G.P.s who are on the Board of Delegates of the State Society to the point where they are willing to cooperate in cutting the throats of the rest of the G.P.s by withdrawing adequate financial support to MINNESOTA MEDICINE.

Under your guidance MINNESOTA MEDICINE has become equal or superior to most journals of national circulation. MINNESOTA MEDICINE has not blindly followed the present fashion to enthrone inductive reasoning as the only kind allowable in the scientific situation and to reduce research to a pebble-pushing sort of scientific reductionism. It has continued to recognize medicine as one of the empiric disciplines in which the theoretical must be tested and proved in the practical situation. In medicine this situation is the clinical.

Under your direction MINNESOTA MEDICINE has continued to support the concept and ideal of patient-oriented medical practice and, therefore, has been the perfect journal for the general practitioner.

Now a group in the traditional hierarchy of our State Society has been persuaded to scupper* this bulwark by the attacks of a self-opinionated, self-complacent, and self-serving group mentioned at the beginning of this letter.

Henry L. Williams, M.D.
West St. Paul, Minnesota

*"Looking Backward from the Twenty-first Century," September, 1970, issue, page 975.

Reprint for Wider Audience

I would like to see a regular column with Letters to the Editor appear in MINNESOTA MEDICINE, as I am sure that there are many comments, agreements and disagreements on the scientific papers and editorials which flutter on your editorial desk and merit publication.

The practice of paring down or omitting altogether the literature references of scientific papers should be discontinued. When the author of a paper compares his work with the results of other published reports it is often quite easy for the experienced reader to understand the gist of the argument at a glance by spotting the all-important "Who, What, Where and When" in the references. An author in anticipation of losing his references may feel compelled to add names, years and footnotes to his text which would be superfluous were he allowed to use references.

The wealth of original scientific papers in MINNESOTA MEDICINE makes me wonder whether or not these publications should not also be read in geographic areas where this state journal is not normally read. The author who elects MINNESOTA MEDICINE as his primary organ of publication finds himself in a dilemma. Either he breaks the unwritten rules of publication ethics and offers his paper to a national or international organ by changing the title, or he may submit the same paper unaltered, which is probably repugnant to Editors of MINNESOTA MEDICINE and of the journal selected for this offer as well. My suggestion for MINNESOTA MEDICINE—with the author's consent—is to automatically submit outstanding papers to specialty journals which would likely be interested in reprinting the article for a wider audience.

H. W. Heupel, M.D., Ph.D.
Minneapolis, Minnesota

You May Be Right (Continued)

Teen-Agers

As the medical director at the Teen-Age Medical Center, 2421 Chicago Avenue, I find it emotionally very rewarding work, with many tears and some very happy moments.

A sixteen-year-old girl came in to determine whether or not she was pregnant. After the examination she was informed that indeed she was. She burst into tears and said, "If I had only gone to the movies with my parents that night, this wouldn't have happened." Then one of the nursing personnel looked at her and said, "My dear, why didn't you go to the movies with your parents that night?" She wept another tear and then said quietly, "They wouldn't let me in. The movie was rated X and no one under 18 was admitted."

We have certainly legislated ourselves into a peculiar situation here. So many of the youngsters that we see are playing a grown-up game and are not old enough to put away their dolls.

Elizabeth B. Jerome, M.D.
Minneapolis, Minnesota

Over-Population Pro

Your notes regarding over-population (in the October issue of MINNESOTA MEDICINE*) are very pertinent and timely. It would be good if more physicians would show more concern for some of the overwhelming social problems such as over-population, which often have some relevance to how medicine should be practiced.

Robert B. Benjamin, M.D.
Minneapolis, Minnesota

*See page 1059.

Over-Population Con

I refer to a small article at the bottom of page 1059, October MINNESOTA MEDICINE. Please do not propagandize us about over-population since we have enough of this in the newspapers. You are entitled to your opinion, but why must we pay these astronomical fees to the State Medical Association to have somebody tell us how bad we are for raising children. In fact, I believe the plot at the bottom of the page must apply to you.

M. F. Lindquist, M.D.
V. A. Sandkamp, M.D.
South St. Paul, Minnesota

In God We Trust

Mark Twain's splenetic remark concerning "trust" (Page 589, May issue of MINNESOTA MEDICINE) should not be left unchallenged. The words "in God we trust" first appeared on a copper coin (the 1864 two-cent piece). The motto did not appear on "silver coins which circulated among the rich" until 1866.

R. M. Petitt, M.D.
Rochester, Minnesota

The Editor's Soliloquy

Regional Journals

No STATE MEDICAL journal can scientifically prosper without an adequate budget. Twenty thousand subscribers would be sufficient to allow a non-profit journal to survive; the revenue from advertising could add prosperity or even affluence.

The state medical journals may be in a so-called "liquidity crisis" wherein many of them are too expensive in time spent and energy expended to make them worthy of publication on the basis of their scientific content. There are many state medical journals that have only one or two scientific articles with a large quantity of bulletin or house organ material scattered among their numerous advertising pages.

Significant progress in medicine is too important to allow it to be buried in a medical journal with only a handful of readers; and the everyday shop talk and local chit-chat of doctors carries no interest for a widely distributed audience.

New medical and scientific developments are simultaneously of interest to the whole medical profession, and there is very little to scoop from each of our own, small, indigenous communities. Even more so than the well-run national news media, which daily dispatch their news over a wide region, limited only by the time required to transport it or by the wave-length that carries it, scientific developments in medicine could be better dispensed by a well-run regional journal on a monthly or bi-weekly basis, relegating local and individually featured items to a more frequent bulletin or mimeographed house organ.

For years, proprietary pride has prevented our sporadic efforts to break the circle of resistance to organized medicine's expensive reduplication of numerous items that could be more economically and efficiently handled as a joint regional venture—as might also be the case with each of our smaller state annual meetings and our individual publications.

As evidenced by the numerous letters received of late* it would be unfortunate indeed if MINNESOTA MEDICINE were allowed to go down the drain unless it could be superseded by something better. A regional journal is not beyond the realm of our capabilities, but it will take some doing.

We are no longer in the horse-and-buggy era of medicine but in a period when scientific and medical information is available to all of us. Unless we are willing to unite our scientific, medical literature efforts over a wider region of distribution, without relying upon such specifics as inadequate captive subscriptions, free journals, medical writers' evaluations, 30-second abstracts, 10-second 6 o'clock news items, and 5-second advertised benefits of one brand of aspirin over another, then we will have to content ourselves with and adjust to whatever the bureaucracies have in store for us.

MINNESOTA MEDICINE has attained an international reputation that is somewhat analogous to the prophet without favor in his own land.**

*See "You May Be Right," Pages 1245-1249.

**Matthew 13:57-58: "And they were offended in him, but Jesus said unto them, 'A prophet is not without honor save in his own country, and in his own house,' and he did not many mighty works there because of their unbelief."

OLD DOC HESS SAYS: It impresses me that we have set aside our books and are fighting a paper tiger, bound firmly with red tape.


Gone with the wind

The gas/acid group of disorders

"The two most common complaints referable to the upper gastrointestinal tract for which patients seek medical relief are hyperacidity and 'gas.' The two often occur together."*

Frees captured gas...neutralizes free acid

SILAIN-GEL Tablets and Liquid are separate formulas designed to provide equivalent dual-action symptomatic relief. Both dosage forms contain simethicone which effectively frees trapped gas, enabling the patient to eliminate it. Magnesium hydroxide in both assures a rapid rise in pH for prompt relief of hyperacidity. The special co-dried aluminum hydroxide/magnesium carbonate gel in the tablets assures the same rapid and uniform reaction rate as the liquid. Thus, both medications achieve prompt and prolonged neutralization of free acid *plus* prompt relief from the pain and pressure of trapped gas.

Always in good taste

The pleasant, distinctive flavor of SILAIN-GEL, as well as its non-constipating feature, make it a therapy your patients can live with—in comfort and without complaint.

Select the form of SILAIN-GEL you want to provide symptomatic relief in: gastric ulcer • duodenal ulcer • heartburn • gastric hyperacidity • gastritis • dyspepsia

when the patient prefers the convenience of a tablet, select
Silain-Gel® Tablets:

when the patient prefers a liquid, select
Silain-Gel® Liquid

Also available for the patient who needs an antifrothicant/antiflatulent agent only: **Silain®** (simethicone) Tablets

*Slanger, A.: Med. Times *94*:150 (Feb.) 1966.

Announcing the "Antgasid"

Silain-Gel®

Tablets: simethicone plus aluminum hydroxide/magnesium carbonate co-dried gel and magnesium hydroxide

Liquid: simethicone plus aluminum hydroxide and magnesium hydroxide

one dose does both: frees captured gas...neutralizes free acid

A·H·ROBINS A.H. Robins Company, Richmond, Virginia 23220

The Doctor

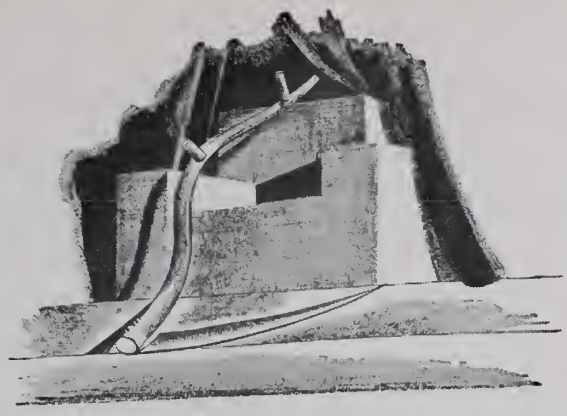
One of the doctor's most important roles is in education.

For his patients, the physician provides the facts, supplies the rationale, triggers the action for life-saving health practices. To his students, he passes on his knowledge and the benefits of his clinical experience. With his colleagues, he shares new information and concepts.

Assisting the doctor in his teaching role is a major function of our professional education program. Through medical conferences, films, exhibits, pamphlets, monographs and other publications, we provide him with the most important and current information on cancer.

If, as Henry Brooks Adams speculated, "A teacher affects eternity; he can never tell where his influence stops", the outlook is optimistic.





In Memoriam

To be born to create, to love, to win at games is to be born to live in time of peace. But war teaches us to lose everything and become what we were not. It all becomes a question of style.
—Albert Camus

REUBEN A. JOHNSON, M.D.

Dr. Reuben A. Johnson, 81, practicing physician in Minneapolis for more than 40 years, died October 6. He had been chief of staff at Abbott Hospital and a clinical professor emeritus, Division of Internal Medicine, University of Minnesota Medical School.

Dr. Johnson was a member of the Academy of Medicine, the Minnesota Society of Internal Medicine, the Minneapolis Society of Internal Medicine, American Medical Association, Hennepin County Medical Society and a Life and 50 Club Member of the Minnesota State Medical Association. He was also the first president of the Minneapolis Society of Internal Medicine.

He is survived by two daughters and a son, Dr. Richard S. Johnson of Edina.

JAMES B. CAREY, M.D.

Dr. James B. Carey, Sr., 75, Minneapolis internist, died August 3. A graduate of the University of Minnesota Medical School, Dr. Carey was a member of the Minnesota Society of Internal Medicine, the Minnesota Academy of Medicine, the American College of Physicians, the Central Society for Clinical Research, the American Gastroenterological Association and former member of the American Medical Association, the Minnesota State Medical Association and the Hennepin County Medical Society.

In 1950 he was president of the American Gastroscopic Society and a member of the Nicollet Clinic from 1921 until his retirement in 1960. He was a former chief of staff of Eitel Hospital and Clinical Associate Professor of Medicine at the University of Minnesota.

He is survived by his wife and two granddaughters.

COURT R. STANLEY, M.D.

Dr. Court R. Stanley, 85, one of the founders of the Worthington Clinic, died September 23. A specialist in the field of eye, ear, nose and throat, Dr. Stanley graduated from the University of Chicago and received his medical degree from Rush Medical College.

He was a member of the Southwestern Minnesota Medical Society, the Hennepin County Medical Society, the American Academy of Ophthalmology and Otolaryngology, the Minnesota Academy of Ophthalmology and Otolaryngology, the American Medical Association, a fellow of the American College of Surgeons, and a Life and 50 Club Member of the Minnesota State Medical Association.

Dr. Stanley is survived by his daughter.

WILLARD C. PETERSON, M.D.

Dr. Willard C. Peterson, 73, Minneapolis surgeon, died August 16. He attended the University of Minnesota and graduated from the University Medical School in 1921. After interning at the Minneapolis General Hospital, Dr. Peterson did postgraduate work at the University of Minnesota and the Mayo Clinic.

He was a fellow of the American College of Surgeons, member of the American Medical Association, Hennepin County Medical Society, Sigma Xi Fraternity and RESA and a 50 Club and Associate Member of the Minnesota State Medical Association.

Dr. Peterson is survived by his wife and two sons, one of whom is Dr. Willard C. Peterson, Jr. of Edina.

JOHN M. FEENEY, M.D.

Dr. John M. Feeney, 76, Minneapolis physician for 45 years, died August 12. Born in Watersmeet, Michigan, Dr. Feeney was a graduate of the University of Wisconsin and of the Northwestern University School of Medicine.

He was a member of the American Medical Association, the American College of Surgeons and the Hennepin County Medical Society and a Life Member of the Minnesota State Medical Association.

Dr. Feeney is survived by his wife and two sons.

FRANK W. CALHOUN, M.D.

Dr. Frank W. Calhoun, 93, Albert Lea obstetrician, died August 13. He had practiced medicine in Albert Lea from 1907 until his retirement.

Born in Indianola, Iowa, Dr. Calhoun attended Simpson College at Indianola and Amity College, College Springs, Iowa and Rush Medical College, Chicago.

He was a member of the American Medical Association, the Freeborn County Medical Society and a 50 Club and Life Member of the Minnesota State Medical Association.

Dr. Calhoun is survived by his wife, four sons and a daughter.

WILLIAM F. CANTWELL, M.D.

Dr. William F. Cantwell, 81, International Falls physician, died August 21. Born in St. Paul, Dr. Cantwell attended St. Paul schools and the University of Minnesota Medical School.

He was chief medical officer for Koochiching County, a member of the American Medical Association and the Range Medical Society, a fellow of the American College

of Surgeons, and a Life Member and 50 Club Member of the Minnesota State Medical Association.

Dr. Cantwell is survived by his wife, four grandchildren and a great-granddaughter.

ROY C. PEDERSEN, M.D.

Dr. Roy C. Pedersen, 61, Duluth physician, died October 3. Born in Duluth, he was a lifelong resident of the city and a graduate of the University of Minnesota Medical School.

He was a former chief of staff at St. Luke's Hospital and a member of the American Medical Association, the Minnesota State Medical Association, the Minnesota Association of Obstetricians and Gynecologists and the St. Louis County and Interurban Medical Societies.

Dr. Pedersen is survived by his wife, four daughters and a son.

ALBERT C. KELLY, M.D.

Dr. Albert C. Kelly, 59, surgical resident at the Veterans Hospital, died November 1. Born in Hibbing, Dr. Kelly attended the Marquette University School of Medicine and practiced medicine in Duluth until 1955 after which he came to St. Paul.

He was a member of the American Medical Association, the Minnesota State Medical Association and the Ramsey County Medical Society.

Dr. Kelly is survived by his wife, two daughters and three sons.

CLIFFORD D. SNYDER, M.D.

Dr. Clifford D. Snyder, Kiester physician for twenty-four years, died October 6. He was fifty-one.

Born in Elmore, Dr. Snyder attended the University of Minnesota Medical School and interned in Fresno, California, at the Fresno General Hospital. He was a member of the American Medical Association, the Minnesota State Medical Association and the Freeborn County Medical Society.

Dr. Snyder is survived by his wife, a daughter, and three sons.

EDGAR J. HUENEKENS, M.D.

Dr. Edgar J. Huenekens, 84, pediatrician and former member of the Minnesota State Board of Health, died July 23. He was a former chairman of the Health Division of the former Council of Social Agencies and had been national medical director of the Sister Elizabeth Kenny Foundation. He was named physician of the year at St. Barnabas Hospital in 1954 and received the Minneapolis Junior Chamber of Commerce's Francis E. Harrington Award in 1957 for public health leadership in the city.

Dr. Huenekens was a member of the American Medical Association and the Hennepin County Medical Society and a 50 Club and Life Member of the Minnesota State Medical Association.

CLARENCE G. OCHSNER, M.D.

Dr. Clarence G. Ochsner, former Wabasha doctor, died September 9, at the age of 63. He had practiced in Wabasha for 28 years.

A graduate of the University of Wisconsin, he specialized in surgery. Dr. Ochsner was a member of the American College of Surgeons, American Medical Association, Wabasha County Medical Society, Minnesota Surgical Society and an Associate Member of the Minnesota State Medical Association.

He is survived by his wife, two daughters, and eight sons, among whom are Dr. John Ochsner of Sioux Falls and Dr. Tom Ochsner of Santa Barbara.

WILLIAM A. PIPER, M.D.

Dr. William A. Piper, Mountain Lake obstetrician, died November 10. He was 88. Born in Bonfield, Illinois, Dr. Piper obtained his medical education at Northwestern University in Chicago and Evanston, Illinois.

He was a member of the Minnesota State Medical Association and the Southwestern Minnesota Medical Society and a Life and 50 Club Member of the Minnesota State Medical Association.

The Human Touch*

'Tis the human touch in this world that counts,
The touch of your hand and mine,
Which means far more to the fainting heart
Than shelter and bread and wine,
For shelter is gone when the night is o'er,
And bread lasts only a day,
But the touch of the hand and the sound of the voice
Sing on in the soul alway.

*Spencer Michael Free (1856-1938), author of some five hundred poems, practiced medicine for almost fifty years in DuBois, Pennsylvania, and specialized in general surgery during his later years. His best known poem, The Human Touch, has been translated into twenty-six languages and quoted widely.

The heights by great men reached and kept
Were not attained by sudden flight,
But they, while their companions slept,
Were toiling upward in the night.

H. W. Longfellow

Classified Advertisements

Classified advertising rates are thirty (30) cents a word; minimum monthly charge $7.50; key number, fifty (50) cents additional.

Replies to advertisements with key numbers should be mailed in care of Minnesota Medicine, 375 Jackson, St. Paul, Minn. 55101.

GENERAL SURGEON needed by established family practice clinic in surburban Minneapolis. Ideal opportunity for well trained surgeon to join this expanding group of young physicians. Income potential above average. Excellent facilities, coverage, and benefit program. Write MINNESOTA MEDICINE—453, 375 Jackson, St. Paul 55101.

NEW EXPANDING OPPORTUNITIES for family physicians and physicians specializing in pediatrics, internal medicine, urology, anesthesiology; in medically-awakening community. Contemporary, automated, 105-bed, new hospital to be completed in the fall of 1970. Present hospital to be converted into long-term unit. Patient service area 50,000 people. Medical staff leading and supporting recruitment efforts. Excellent community location, forty miles equi-distant to Milwaukee or Madison. Complete educational, cultural and recreational facilities. A new medical-dental building and 130-bed skilled care nursing home being constructed adjacent to the new hospital ready for occupancy January, 1971. Immediate satisfaction in practice, income and family living. Special assistance if needed. Write or call Paul R. Glunz, M.D., Watertown Memorial Hospital, 1301 E. Main Street, Watertown, Wisconsin 53094; telephone 414-261-4210 for more information.

G. P. WANTED: Permanent position or Locum Tenens. Clinic serving population area of 12,000. City has new hospital, new clinic building; new swimming pool; metropolitan city near. Write or call Warren Clinic, Warren, Minn. 56762. 742-6231, area code 218.

WE ARE seeking a board eligible or board certified pediatrician to join a 5-man group located in the scenic St. Croix Valley area of Wisconsin, 15 miles from the Twin Cities. Please call me collect at any time so that I may offer you further details. M. A. Cornwall, M.D. 715-386-2311.

GENERAL PHYSICIAN wanted to join two well established family doctors, suburb Minneapolis area. Finest facilities. Early partnership Finest hospital facilities. Doctors Bloedel and Ransom, Osseo 55369. Call 612-425-2117.

"GENERAL PRACTITIONER OR INTERNIST to join congenial four man group. Partnership available in one year. Laboratory and x-ray facilities. Donald W. Koza, M.D., 1239 Payne Avenue, St. Paul, Minn. 55101. Call: (612) 771-5577."

GP-INTERNIST WANTED for growing Wisconsin community, outstanding opportunity, patient service area exceeds 10,000—desirable location for family living—good schools—doorway to Horicon Recreational area. Contact: Executive Secretary, Mayville Chamber of Commerce, Box 86, Mayville, Wisconsin 53050.

GENERAL PRACTITIONER wanted to join well-established practitioner. New clinic building—90 miles east of St. Paul—city of 14,000. Early partnership with full hospital facilities. Ideal location. L. W. Picotte, M.D., Chippewa Falls, Wisconsin.

ADAMS CLINIC, P. A., a long established medical group in Hibbing in Northern Minnesota offers excellent income, profit sharing retirement benefits, life and health insurance, a new building only two blocks from a modern well staffed hospital in an atmosphere free from pollution and strife. The Clinic wishes to add a Board Certified or Board Eligible Surgeon, Orthopedic Surgeon, Internist, and General Practitioner. The community has a drawing area technical school, a junior college and recreational opportunities in all directions. An ideal place to raise a family. Only three hour drive to Twin Cities. Will pay expenses for an interview. Phone—(218) 262-3425.

INTERNIST AND GENERAL PRACTITIONER wanted to join a five-man clinic group in Minneapolis. Complete laboratory and X-ray with board roentgenologist. Excellent hospital staff associations. Salary arrangement to start with, early partnership. Write MINNESOTA MEDICINE—289; 375 Jackson, St. Paul 55101.

GENERAL PRACTITIONER wanted for four man group with Board surgeon associated with community sponsored prepayment plan in NE Minnesota; hay fever haven; accredited hospital with radiologist, pathologist & internist services next door to modern clinic; good schools, swimming pool, indoor ice arena, golf, hunting, fishing, liberal salary $22,000-$25,000 first year; full partnership 6 months; equitable rotating call schedule & immediate work load. Write Medical Director, Community Clinic, Two Harbors, Minnesota 55616.

GP AND OB GYN wanted to join two GPs, surgeon, and internist in suburban group. Excellent nearby hospital. Salary first year, then partnership. Write MINNESOTA MEDICINE—436, 375 Jackson, St. Paul 55101.

WANTED: Young physician for association leading to partnership with four well established General Practitioners in fast growing suburb of St. Paul. Excellent clinic facilities in nearly new, partnership owned, well equipped, medical center building. Write: MINNESOTA MEDICINE—421, 375 Jackson, St. Paul 55101.

GENERAL PRACTITIONER to join well established two-man general practice group. Well equipped clinic. 15 minutes to Minneapolis. Contact: C. W. Zinn, M.D. 612-473-7364.

WANTED: General practitioners, Internist, Pediatrician, Orthopedic Surgeon, Obstetrician and Gynecologist for the Bemidji Clinic of Bemidji, Minnesota. Outdoor sports advantage second to none. The Bemidji Clinic now consists of three general practitioners, one internist, two general surgeons, one obstetrician, one otolaryngologist, and one ophthalmologist. If interested contact Duane E. Carlson, Business Manager, Bemidji Clinic, Bemidji, Minnesota.

(Continued to page 1258)

Classified Advertisements

(Continued from page 1257)

A 5-MAN GROUP located in the scenic St. Croix Valley area of Wisconsin, 15 miles from the Twin Cities, is seeking a qualified physician in the field of internal medicine, and also a general practitioner. Please call me collect at any time so that I may offer you further details. M. A. Cornwall, M.D. 715-386-2311.

INTERNIST AND PEDIATRICIAN WANTED—Group of two general surgeons and one obstetrician-gynecologist looking for board qualified or certified internist and pediatrician. We are creating a partnership of young well trained physicians in a mutual complimentary practice. Incorporation is in process with excellent fringe benefits. We are located in north central Wisconsin serving a community of approximately 25,000 with a summer population of 200,000. We have excellent recreational and educational facilities including college. Starting salary is $25,000 with partnership after one year. Anyone interested write to Dr. I. E. Schiek, Jr., c/o The Schiek Clinic, Rhinelander, Wisconsin 54501 or call collect 715-362-6160.

ST. PAUL—Spacious medical suite in new split-level building, part of a one block medical-dental complex adjacent to large shopping center. 1504 White Bear Avenue (612) 774-7144.

PHYSICIAN available weekends through December and for longer intervals thereafter—general practice or emergency room. Write Peripatetic Physician, P.O. Box 792, Rochester, Minn. 55901.

TIRED OF THE RAT RACE??? Join us in comfortable country living fifty miles north of Minneapolis. Opening in new modern clinic building just completed for one or two general practitioners to initiate their own practice or affiliate with local M.D. Nominal rent to assist young practice, 25,000 population within 15 miles radius, city has dental-veterinary-mental health clinics, 20 bed hospital. Golfing, bowling, fishing, hunting, etc. Expenses for personal interview will be allowed. Contact: Harold Casebeer, Adm. Braham Community Hospital 396-3331; Randall LaKosky, M.D., Med. Dir. Mental Health Center 396-3333, Braham, Minnesota 55006.

MEDICAL OFFICES AVAILABLE—Desirable Edina location. Four examining rooms—two laboratories—private office—waiting room and nurses' office. Air-conditioned—elevator. Adequate free parking. Contact George Kruse (612) 922-8691 or Karl W. Pleissner, M.D. (612) 339-4801.

TEN MAN MULTISPECIALTY group needs an ophthalmologist and another pediatrician. New clinic building, complete laboratory and x-ray facilities. 180 bed modern hospital across street from clinic. Early share-holder status. Salary open. Write or call the Lenont-Peterson Clinic, Ltd., C. A. Tietz, M.D., area code 218, 741-4292, Virginia, Minnesota 55792.

IMMEDIATE OPENING: Internist or General Practitioner to join six man multispecialty group in northeastern Wisconsin. Excellent professional opportunity to practice in a friendly community, only two actively practicing physicians (General Practitioners) in the community outside of our clinic. Salary commensurate with training and experience first year and then full partnership. Ideal, safe small city living for the family on scenic Lake Michigan with excellent fishing, boating and hunting. All this and still only 1½ hours drive to Milwaukee or 45 minutes to Green Bay or lovely Door County. For complete details contact Robert E. Myers, M.D., Garfield at 23rd, Two Rivers, Wisconsin 54241.

CLINICAL CORPSMAN to assist G.P.-U.S.N., graduating December Cleveland Clinic one year program. Robert Nims, 5144 E. Farnhurst Rd., Lyndhurst, Ohio 44124.

EXPANDING GROUP needs General Practitioner, Internist. Competitive salary, fringe benefits, partnership opportunity. New Clinic, 150 bed fully accredited hospital metropolitan area. J. E. Brown, M.D., 555 Simpson, St. Paul, Minn. 55104. Phone (612) 645-9406.

GENERAL PRACTITIONER wishes an associate in southern California, West San Fernando Valley. Contact: Robert A. Elliot, M.D., 22554 Ventura Blvd., Woodland Hills, California 91364. Phone 213-883-9090 collect.

COLLEGE HEALTH SERVICE PHYSICIAN: General Practitioner needed for 4,500 student lakeshore state college in Northern Minnesota lake country. Hours and salary by negotiation. For information send vitae to Dr. C. J. Kemper, Vice President for Student Affairs, Bemidji State College, Bemidji, Minnesota.

Established three-man group needs physician to provide full-time coverage. Guaranteed annual wage—health and accident insurance—pension plan, Minnesota license required. Write or call Drs. Fisketti or Parson—St. Luke's Hospital—Duluth, Minnesota 55805. Telephone 218-727-6636.

OB/GYN-PEDIATRICIAN-INTERNIST Mpls.-St. Paul. Midwest's leading prepaid group offers high standards, excellent earnings, no investment. Generous vacation and conference leave, fully paid insurance and retirement, time for teaching and professional pursuits. A. F. Anderegg, M.D., 612-645-5851, 2500 Como Ave., St. Paul, Minnesota 55108.

FULL-TIME PHYSICIANS NEEDED for staff approved in-hospital emergency coverage in 600 bed hospital. Active medical, surgical, pediatric & obstetrical services with ICU & CCU departments. Guaranteed annual wage—health & accident insurance—pension plan. Minnesota license required. Write or call Drs. Fisketti or Parson or Mr. R. Fox, Administrator—St. Luke's Hospital—Duluth, Minnesota 55805. Telephone 218-727-6636.



The concert was just underway,
When to the conductor's dismay
Cramps and diarrhea,
Did so quickly appear,
The maestro no longer could stay.

Because diarrhea with cramping, nausea, and painful straining can strike at the most inopportune time, it takes a comprehensive agent to treat the total diarrheal syndrome and help get the patient back on the job. That's why so many physicians rely on Donnagel, especially during the fall and winter months when "flu" and viral gastroenteritis usually hit their peak.

Donnagel is much more than just a simple kaolin-pectin combination. It also contains the belladonna alkaloids to calm GI hypermotility and help relieve the distressing discomforts which so often accompany diarrhea. Certainly it's less expensive and more convenient than taking two medications. And the dosage is lower too. Available in the handy 4-oz. plastic bottle at pharmacies everywhere on your prescription or recommendation.



When diarrhea and its discomforts separate a man from his job . . .

Donnagel®

Each fluid ounce contains: Kaolin, 6 g.; Pectin, 142.8 mg.; Hyoscyamine sulfate, 0.1037 mg.; Atropine sulfate, 0.0194 mg.; Hyoscine hydrobromide, 0.0065 mg.; Sodium benzoate (preservative), 60 mg.; Alcohol, 3.8%.

A·H·ROBINS

A. H. Robins Company,
1407 Cummings Drive,
Richmond, Va. 23220

Coughs are back.



clear the tract with the

Robitussin® Line

The coughing season is here again. Time to rely on the four Robitussins and Cough Calmers to help clear the lower respiratory tract. All contain glyceryl guaiacolate, the efficient expectorant that works systemically to help increase the output of lower respiratory tract fluid. The enhanced flow of less viscid secretions soothes the tracheobronchial mucosa, promotes ciliary action, and makes thick, inspissated mucus less viscid and easier to raise. Available on your prescription or recommendation.

For coughs of colds and "flu"

Robitussin®

Each 5 cc. contains:

Glyceryl guaiacolate	100.0 mg.
Alcohol, 3.5%	

For unproductive allergic coughs

Robitussin A-C®

Each 5 cc. contains:

Glyceryl guaiacolate	100.0 mg.
Pheniramine maleate	7.5 mg.
Codeine phosphate	10.0 mg.
(warning: may be habit forming)	
Alcohol, 3.5%	

Non-narcotic for 6-8 hr. cough control

Robitussin-DM®

Each 5 cc. contains:

Glyceryl guaiacolate	100.0 mg.
Dextromethorphan hydrobromide	15.0 mg.
Alcohol, 1.4%	

Clears sinuses and nasal stuffiness as it relieves cough

Robitussin-PE®

Each 5 cc. contains:

Glyceryl guaiacolate	100.0 mg.
Phenylephrine hydrochloride	10.0 mg.
Alcohol, 1.4%	

Robitussin-DM in solid form for "coughs on the go"

Cough Calmers™

Each Cough Calmer contains:

Glyceryl guaiacolate	50.0 mg.
Dextromethorphan hydrobromide	7.5 mg.

Select the Robitussin® "Clear-Tract" Formulation That Treats Your Patient's Individual Coughing Needs:

Robitussin® extra benefit chart

All 5 Robitussins have an EXPECTORANT-DEMULCENT action. Keep this handy chart as a guide in selecting the formula that provides the *extra* benefits you want for your patient.

	Cough Suppressant	Antihistamine	Long-Acting (6-8 hours)	Nasal, Sinus Decongestant	Non-Narcotic
ROBITUSSIN®					●
ROBITUSSIN A-C®	●	●			
ROBITUSSIN-DM®	●		●		●
ROBITUSSIN-PE®				●	●
COUGH CALMERS™	AHR		AHR		AHR

A. H. Robins Company, Richmond, Va. 23220 A·H·ROBINS

PUBLISHED TO REPLACE A PREVIOUS ADVERTISEMENT WHICH THE FOOD AND DRUG ADMINISTRATION CONSIDERED MISLEADING

The Food and Drug Administration has requested that we bring to your attention a recent promotional campaign for Garamycin Injectable (gentamicin sulfate) which featured a nationwide *in-vitro* hospital survey involving a comparison of sensitivity patterns of Garamycin Injectable and seven other antibiotics.

The FDA considers the advertising misleading in several respects such as:

The *in-vitro* chart contained in the ads, which compared Garamycin Injectable with seven other antibiotics, implied that Garamycin Injectable is clinically more effective than the seven other compared antibiotics. THE FACTS ARE (1) THAT DIRECT EXTRAPOLATION OF NONCLINICAL FINDINGS TO CLINICAL EFFECTIVENESS IS UNWARRANTED, AND (2) THAT THE ADVERTISED *IN-VITRO* COMPARISONS DO NOT CONSTITUTE A VALID BASIS FOR SUGGESTING THAT GARAMYCIN INJECTABLE HAS GREATER CLINICAL EFFECTIVENESS THAN THE COMPARED ANTIBIOTICS.

The *in-vitro* chart and information contained under the ad heading, "Indications" presented *in-vitro* data results in such a way as to imply that the drug is indicated for Gram-positive bacteria, such as *Staphylococcus aureus*. GARAMYCIN INJECTABLE IS NOT APPROVED FOR INFECTIONS DUE TO ANY GRAM-POSITIVE ORGANISMS.

We emphasize that Garamycin Injectable is approved for use only in infections due to susceptible strains of gram-negative bacteria, including Pseudomonas aeruginosa, and species of indole-positive and indole- negative Proteus, Escherichia coli, and Klebsiella-Aerobacter.

Injectable Garamycin®

brand of gentamicin sulfate injection

Schering

Each cc. contains gentamicin sulfate equivalent to 40 mg. gentamicin

BRIEF SUMMARY

INDICATIONS GARAMYCIN Injectable is clinically effective in infections due to susceptible strains of gram-negative bacteria, including Pseudomonas aeruginosa, and species of indole-positive and indole-negative Proteus, Escherichia coli, and Klebsiella-Aerobacter. Bacteriologic studies should be conducted to identify the causative organism and to determine its sensitivity to gentamicin sulfate. Sensitivity discs of the drug are available for this purpose. If the susceptibility tests indicate that the causative organism is resistant to gentamicin sulfate, other appropriate antibiotic therapy should be instituted.

This drug should be limited to the treatment of serious infections caused by gram-negative bacteria, particularly Pseudomonas aeruginosa, Proteus and other susceptible organisms, with due regard for relative antibiotic toxicity. Therefore, the drug should be considered for use against gram-negative: 1. Bacteremia; 2. Infected surgical wounds; 3. Severe soft tissue infections, including burns complicated by sepsis; 4. Respiratory tract infections; and 5. Selected cases of urinary tract infection.

CONTRAINDICATIONS GARAMYCIN Injectable is contraindicated in individuals with a history of hypersensitivity or toxic reactions to gentamicin.

WARNINGS Patients receiving treatment with GARAMYCIN should be under close clinical observation because of the toxicity associated with the use of this drug. Ototoxicity, vestibular and auditory, can occur in patients, primarily those with pre-existing renal damage, treated with GARAMYCIN Injectable, usually for longer periods or with higher doses than recommended.

GARAMYCIN Injectable is potentially nephrotoxic, and this should be kept in mind when it is used in patients with pre-existing renal impairment. Kidney function diminished by infection of the upper urinary tract may, however, improve during effective treatment with GARAMYCIN Injectable.

Concurrent administration of potentially ototoxic drugs such as streptomycin and kanamycin or of potentially nephrotoxic drugs such as polymyxin, colistin, and kanamycin with gentamicin sulfate has not been shown to afford any clinical advantages and, moreover may result in additive toxicity. Monitoring of vestibular, cochlear, and renal function will provide guidance for therapy in such cases.

PRECAUTIONS In patients with impaired renal function in whom serious infection develops, serum concentrations of the drug may rise, with consequently increased risk of ototoxicity. In these patients or in those in whom recommended dosage or duration of therapy must be exceeded as a life-saving measure, routine studies of kidney function should be performed when possible. These may be supplemented by evaluation of the vestibular and auditory function and measurement of serum concentration of the drug when feasible. Serum concentration of gentamicin should be maintained below the range of 10-12 mcg./ml. to reduce risk of ototoxicity.

Ordinarily, treatment should not be given for more than 7 to 10 days or be repeated unless required for serious infection not responsive to other agents.

As with other antibiotics, treatment with GARAMYCIN Injectable may occasionally result in overgrowth of nonsensitive organisms. If superinfection occurs, appropriate therapy is indicated.

Safety for use in pregnancy or the potential for fetal ototoxicity or nephrotoxicity have not been established. Studies in pregnant animals have not revealed teratogenic or ototoxic effects in the fetus. GARAMYCIN Injectable should not be used in pregnant patients or in women of childbearing age unless its use is deemed advisable by the physician.

ADVERSE REACTIONS The overall incidence of ototoxicity considered related to treatment with GARAMYCIN Injectable was 2.8 per cent (16 of 565 patients). Contributory factors (two or more factors were relevant to most patients) were as follows: 10 had azotemia, 10 received a total of 1 gram or more of the drug, 7 had recently received other potentially ototoxic antibiotics (streptomycin or kanamycin), and 5 were over 60 years of age. Six also had decreased high-tone hearing acuity, which returned to or toward normal in the 4 patients retested.

Analysis of BUN data indicated that 4 (2%) of 172 patients showed increases in BUN that were probably related to treatment with GARAMYCIN Injectable. Of 20 increases probably or possibly related to treatment, 7 were reversible, 9 occurred in terminal patients, and 4 had no follow-up.

Other adverse reactions associated with treatment were one instance each of urticaria, decreased hematocrit, and reversible depression of granulocytes with normal bone marrow. Other rarely reported and possibly treatment-related adverse reactions were anemia, increased reticulocyte count, rash, purpura, drug fever, hypotension, convulsions, twitching, salivation, nausea, vomiting, increased transaminase activity (SGOT or SGPT), increased serum bilirubin, decreased serum calcium, and joint pain.

PACKAGING GARAMYCIN Injectable, 40 mg./cc., 2-cc. multiple-dose vials, for intramuscular administration.

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March 18-20 ..... Office Management of the Emotionally Disturbed Patient
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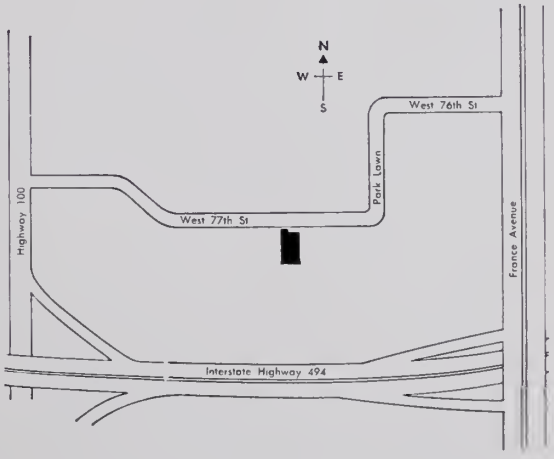
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